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The functional anatomy of working memory training using chunking in Alzheimer's disease

Huntley, Jonathan David

Awarding institution:
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**THE FUNCTIONAL ANATOMY OF WORKING MEMORY
TRAINING USING CHUNKING IN ALZHEIMER'S DISEASE**

Jonathan Huntley

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University of London

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ABSTRACT

AIMS

A randomised controlled trial of a novel cognitive training regime based on chunking was conducted in participants with early Alzheimer's Disease. Functional neuroimaging was performed to examine re-organisation of brain activity following cognitive training. The study tested the following hypotheses:

- 1) Training individuals with early AD in the use of chunking strategies would improve their working memory (WM) capacity.
- 2) Following training in chunking, improvement in WM capacity would generalise across different modalities of WM tasks and measures of general cognitive functioning.
- 3) Improvement in WM capacity following cognitive training would be associated with re-organisation of functional activity in the prefrontal cortex (PFC) and posterior parietal cortex (PPC).

METHODS

30 patients with early AD were recruited and assessed on WM and general cognitive tasks. They also performed a verbal WM chunking task whilst undergoing fMRI. They were then randomised to either an active control group or cognitive training group. The cognitive training group had 18 sessions of adaptive WM training using chunking strategies, whilst the control subjects practised a non adaptive WM task. All subjects were then reassessed using the same measures of cognitive function, WM and fMRI protocol, allowing the above hypotheses to be tested.

RESULTS

At baseline, all participants benefitted from chunking to improve WM ($p < 0.001$). Following training, the training group demonstrated a significant improvement on the chunking WM task ($p < 0.05$) compared with the control group. There were also significant improvements in measures of general cognitive function (MMSE and ADAS-Cog) and verbal episodic memory in the training group compared to controls ($p < 0.05$). Training was significantly associated with a reduction in activation in the PFC-PPC network following cognitive training.

DISCUSSION

The impact of this novel approach to improving WM in early AD is discussed, in the context of existing knowledge of cognitive training and functional plasticity in AD.

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ABBREVIATIONS

AC/PC	Anterior Commissure/ Posterior Commissure
ACC/SMA	Anterior Cingulate Cortex/Supplementary Motor Area
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive section
ANOVA	Analysis of Variance
BOLD	Blood Oxygen Level Dependent
BPSD	Behavioural and Psychological Symptoms of Dementia
CI	Confidence Interval
CONT	Control Group
CR	Cognitive Rehabilitation
CS	Cognitive Stimulation
CT	Cognitive Training
DARTEL	Diffeomorphic Anatomical Registration Through Exponential Lie Algebra
DEMqoL	Dementia Quality of Life questionnaire
DLPFC	Dorso-Lateral Prefrontal Cortex
EPI	Echo Planar Imaging
fMRI	Functional Magnetic Resonance Imaging
FWHM	Full Width at Half Maximum
GDS	Geriatric Depression Scale
GLM	General Linear Model
GR	Grammatical Reasoning
IOP	Institute of Psychiatry
IQ	Intelligence Quotient
JH	Jonathan Huntley
LDLPFC	Left Dorso-lateral Prefrontal Cortex
LPC	Left Parietal Cortex

MarsBar	MARSeille Boîte À Région d'Intérêt
MCI	Mild Cognitive Impairment
MCID	Minimum Clinically Important Difference
MCTS	Mixed Cognitive Training and Stimulation
MD	Multiple Demand
MEDS	Medication
MIA	Meta-memory in Adulthood questionnaire
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
MP-RAGE	Magnetization-Prepared Rapid Gradient-Echo
MRI	Magnetic Resonance Imaging
NA	Non Active control group
NART	National Adult Reading Test
NPI	Neuropsychiatric Inventory
OOO	Odd One Out Test
PPC	Posterior Parietal Cortex
PPI	Psycho-physiological interactions
RAIFO	Right Anterior Inferior Frontal area
RCT	Randomised Controlled Trial
RDLPFC	Right Dorso-Lateral Pre – Frontal Cortex
ROI	Region of Interest
RPC	Right Parietal Cortex
SD	Standard Deviation
SEM	Standard Error of the Mean
SMD	Standardised Mean Difference
SOS	Self Ordered Search Task
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
T	Tesla
TE	Echo Time

TR	Repetition Time
TRAIN	Training Group
TSDiffAna	Time Series Difference Analysis
VBM	Voxel Based Morphology
VOI	Volumes of Interest
WM	Working Memory

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Chapter 1 INTRODUCTION

1.1 ALZHEIMER'S DISEASE (AD) - EPIDEMIOLOGY

Dementia is characterized by progressive cognitive impairment. It is estimated that currently 44.35 million people suffer from dementia worldwide with numbers predicted to increase to 135.46 million by 2050¹. Aside from the enormous personal and societal costs of the disease, in 2010 the global financial cost of dementia was estimated at US\$604 billion².

There are currently no disease modifying treatments and current licensed pharmacological agents provide only modest symptomatic cognitive and functional benefits³. There is therefore a clear and urgent need for efficacious, evidence - based therapies to help stabilise or improve cognitive function in those suffering from dementia.

1.2 DIAGNOSIS AND FEATURES OF AD

Alzheimer's disease (AD) is the most common form of dementia⁴. A diagnosis of Alzheimer's disease requires a history of insidious onset and gradual progression, impairment of two or more cognitive domains and impaired instrumental activities of daily living⁵. AD may also present with non-cognitive neuropsychiatric symptoms and leads to significant functional and social impairment. A summary of recently updated diagnostic guidelines for AD is shown in Table 1-1.

CORE CLINICAL FEATURES OF DEMENTIA
Decline from previous levels of functioning, not explained by delirium or major psychiatric disorder
Cognitive impairment assessed through a combination of history taking and objective assessment
Cognitive or behavioural impairment involves a minimum of two of:
A) Impaired ability to acquire and remember new information
B) Impaired reasoning and handling of complex tasks, poor judgement
C) Impaired visuospatial abilities
D) Impaired language function (speaking, reading, writing)
E) Changes in personality, behaviour or comportment
PROBABLE AD
1) Meets criteria for dementia
2) Insidious onset (gradual onset over months to years)
3) History of worsening of cognition by report or observation
The initial and most prominent cognitive deficits are either:
A) Amnesic presentation- impairment in learning and recall. Plus evidence of dysfunction in at least one other cognitive domain
B) Non-amnesic presentations: - prominent deficits in a) language, b) visuospatial function, c) executive function. Plus evidence of dysfunction in at least one other cognitive domain
There should not be evidence of
- Substantial concomitant cerebrovascular disease
- Core features of other forms of dementia (Lewy Body Dementia, Fronto-temporal dementia, semantic dementia or primary progressive aphasia)
- Evidence for another concurrent, active neurological disease or medical co morbidity, or use of medication that could have a substantial effect on cognition
Increased certainty is provided by:
- Documented evidence of progressive cognitive decline
- Evidence of a causative AD genetic mutation
- Biomarker evidence of the AD pathophysiological process: (low CSF A β ₄₂ , positive PET amyloid imaging, elevated CSF tau, decreased FDG uptake on PET in temporo-parietal cortex; disproportionate temporal atrophy on structural MRI)
Possible AD - diagnosis made in circumstances of:
- Atypical course, or
- Etiologically mixed presentation- meets core criteria for AD plus evidence of
- a) concomitant cerebrovascular disease or features of DLB
- b) evidence for another neurological disease, medical co morbidity or medication use

Table 1-1 Diagnostic criteria for Alzheimer's disease
Adapted from McKhann et al 2011⁶

As shown in Table 1-1, a diagnosis of AD is either 'probable', or 'possible', and a diagnosis of definite AD requires post mortem evidence of neuropathological features, including amyloid plaques and neurofibrillary tangles⁷.

Over the last 20 years there has been an increasing recognition and characterisation of a pre-dementia state, classified as mild cognitive impairment (MCI)⁸. This describes individuals with subjective and objective evidence of cognitive impairment, in the absence of functional decline. A summary of the diagnostic features of MCI is presented in Table 1-2. Potential progression of MCI to dementia remains unclear, with different studies finding between 6% and 34% of MCI subjects progressing to AD over follow up times of 1-5 years⁹⁻¹¹. However increased prognostic confidence is associated with differentiating cases of MCI with underlying Alzheimer's pathology from alternative causes¹².

MCI CRITERIA
1) Concern regarding deterioration in cognition
2) Impairment in one or more cognitive domains (typically 1-1.5 SDs below the mean for age and education) Impairment can occur in a variety of cognitive domains, including memory, executive function, attention, language and visuospatial skills
3) Preservation of independence in functional abilities
4) No dementia - cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning
Features of MCI consistent with AD patho-physiological process:
- No vascular, traumatic or medical causes of cognitive decline
- Evidence of longitudinal decline in cognition
- History consistent with AD genetic factors

Table 1-2: MCI diagnostic criteria
Adapted from Albert et al 2011¹²

The most commonly described area of cognition affected in AD is episodic memory. It has been suggested that early episodic memory impairment is a core diagnostic feature of AD¹³. Episodic memory can be defined as 'storage and retrieval of temporally dated, spatially located and personally experienced events or episodes, and temporal-spatial relations among such events' ¹⁴.

As the diagnostic criteria indicate, deficits are also seen in other areas of cognitive function, including executive function, visuo-spatial function, language, attention and working memory.

1.3 THE WORKING MEMORY (WM) MODEL

The working memory (WM) model of short - term memory was described by Baddeley and Hitch in 1974¹⁵. The original model described modality-specific subsidiary systems: the 'phonological loop' which holds verbal information; and the 'visuospatial sketchpad' which holds visual images. These subsidiary systems are under the control of a 'central executive system' which allows for executive control of information within WM^{16 17}. Several cognitive roles have been attributed to the central executive, including shifting and dividing attention, inhibition of irrelevant information and manipulation of verbal and visual information within the subsidiary systems^{16 18}. A further component, the 'episodic buffer', was added to the model in 2000, to account for experimental findings including the improved recall seen with grouping or chunking information, which may require integration of information from episodic memory. The inclusion of the episodic buffer into the model placed WM at the interface between episodic memory and executive function¹⁹.

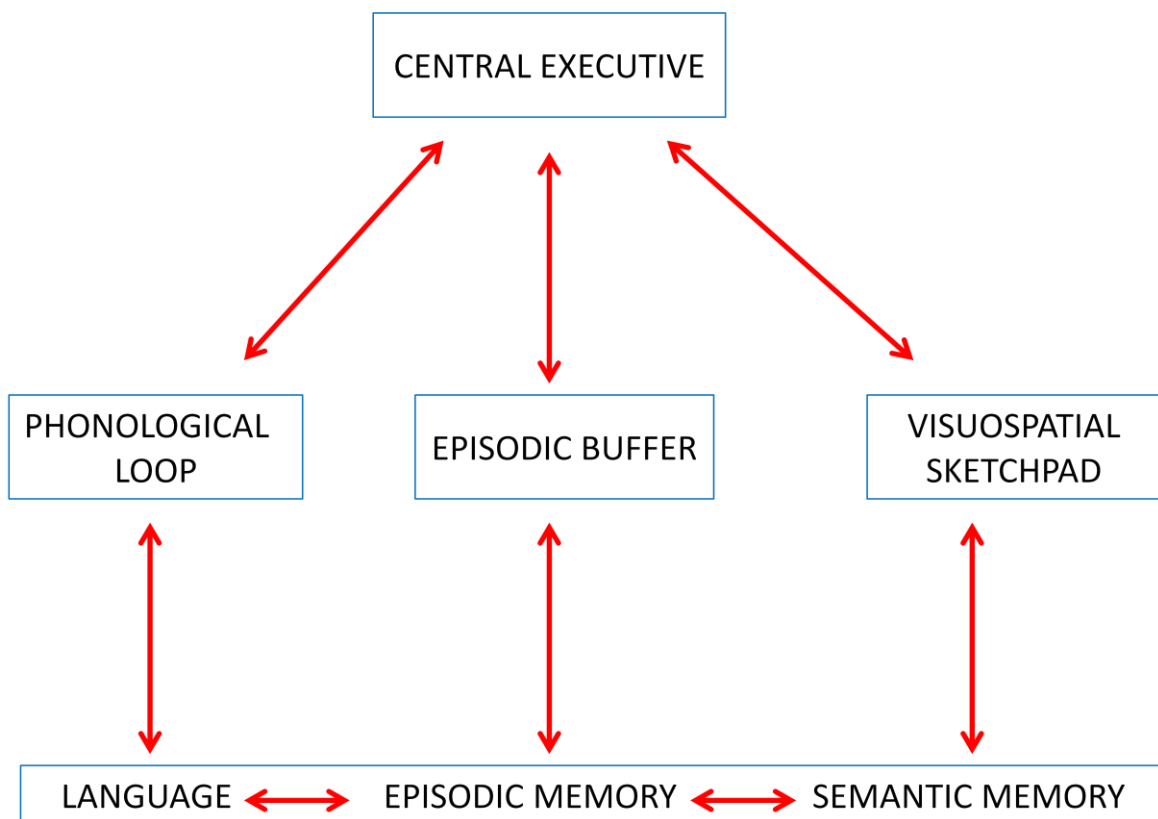


Figure 1-1: Schematic diagram of components of working memory model
Adapted from Baddeley (2000)¹⁹

1.4 WORKING MEMORY AND AD

Although deficits in episodic memory characterise Alzheimer's disease (AD), there is increasing evidence that WM is also impaired at the earliest stages of the disease¹⁷. The ability to hold and manipulate information over short periods of time in WM is essential for many cognitive processes. WM deficits in AD have been associated with difficulties in many everyday tasks and executive control of WM is particularly sensitive to the disease^{20 21}. Using executive strategies to encode information is important in WM performance and learning, and there is some evidence that use of such strategies is impaired at the mild stage (e.g. MMSE 18-23) but preserved at the earlier 'minimal' stage (e.g. MMSE > 24) of AD²².

1.5 CHUNKING STRATEGIES IN WM

It has been demonstrated that WM has a limited capacity²³, therefore strategies are often employed to improve the amount of information that can be held or manipulated within WM. A common and effective strategy is chunking. Chunking is a form of strategic encoding which involves the recoding of a set of data into a compressed, efficient form and can extend WM capacity²⁴⁻²⁶.

A number of verbal and spatial WM tasks have been developed that encourage the reorganization of information into higher level chunks^{24 26}. Both digit and spatial span sequences are presented in either structured or random forms. Structured sequences of digits to be learned are presented as runs of ascending or descending adjacent, even or odd numbers. Therefore within, for example a 6 digit trial of '2 4 6 9 7 5', there is a sequence of three ascending even numbers, followed by a descending group of three odd numbers. This intrinsic structure within the span sequence encourages the grouping or 'chunking' of the digits into two blocks of three, thus allowing more information to be held in WM. In contrast, random sequences are designed to have no obvious associations between digits, making chunking relatively more difficult.

In structured spatial sequences every location is either presented in the same column, row or diagonal as the preceding location. Therefore, the sequence follows identifiable shapes or patterns that can be chunked. In contrast, unstructured sequences follow no such pattern and are designed to be as random as possible (Figure 1-2).

Previous studies have demonstrated that structured stimuli significantly encourage chunking, lessening WM demand and significantly improving WM performance^{24 26 27}.

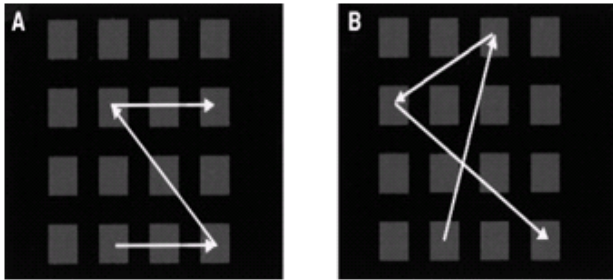
Verbal Span Sequences	Spatial Span Sequences
<p>A) 2 4 6 9 7 5</p> <p>B) 8 1 6 2 9 4</p>	

Figure 1-2: Examples of structured (A) and random (B) digit and spatial span sequences. Structured sequences encourage chunking of span items to improve recall.

1.6 NEURAL BASIS OF WM: FUNCTIONAL NEUROIMAGING

Animal²⁸⁻³¹ and human studies have demonstrated that encoding, storage and retrieval of information in WM is associated with activity in the prefrontal cortex (PFC) and posterior parietal cortex (PPC). Many of these studies utilised functional neuroimaging to investigate the neural correlates of cognitive function, and functional magnetic resonance imaging (fMRI) is one of the most commonly used methods.

In brief, fMRI is based on the principle that the magnetic resonance of haemoglobin differs according to its oxygenation state. Neuronal activity requires oxygen, and therefore there is an increase in blood flow and delivery of oxygenated haemoglobin, which subsequently shifts to a deoxygenated state with increased activity. The difference in magnetic resonance associated with the change in oxygenation state can be measured, as the Blood Oxygen Level Dependent (BOLD) signal. Several assumptions are made when fMRI is used to measure cognitive processes. The main assumption is that the BOLD signal correlates with underlying neural activity. The exact relationship between electrical activity at a neural level and BOLD signal remains unclear³², and there is a temporal delay between neural activity and the BOLD response. Therefore during analysis the BOLD response has to be modelled onto the time series of the cognitive events under investigation. Over the last 20 years, both the quality of images due to increasing magnetic strength and improved signal-to-noise ratios, and the sophistication of analysis tools have allowed increasingly accurate mapping of cognitive processes to underlying brain activity.

Echo planar imaging allows the collection of data from the whole brain over a few seconds³³. This allows improved temporal resolution of functional brain imaging and combined with event-related experimental designs enables more sophisticated and specific analysis of cognitive processes.

A well-established analysis tool for fMRI data is Statistical Parametric Mapping (SPM)³⁴. This software package provides modules for temporal and spatial pre-processing of raw data, to correct for movement and register all images into normalised three-dimensional space. SPM uses the general linear model to convolve the BOLD response with the experimental time series and produces a study design matrix using conditions of interest. Contrasts between conditions of interest can then be analysed statistically. Random effects analysis allows examination of statistical differences between conditions of interest at a group level, where inferences about the neuroanatomical correlates of the cognitive function under investigation can be made.

1.7 FUNCTIONAL NEUROIMAGING OF WORKING MEMORY

Functional imaging studies have identified the possible neurological correlates of both the subsidiary systems and executive components of the WM model. The phonological system has been linked to left supramarginal gyrus and speech areas^{35 36}. The visuospatial system has been associated with activity in a range of frontal, parietal and occipital regions^{37 38}. FMRI studies have also sought to identify the neurological correlates of central executive function. Several groups have identified activation in dorsolateral prefrontal cortex (PFC) and left posterior parietal cortex (PPC) during the executive control of information within verbal WM³⁹⁻⁴², demonstrating the importance of the PFC in WM tasks requiring executive control^{40 43 44}. A confounding factor has been the observed increase in PFC activity with increasing task difficulty⁴⁵. A series of fMRI studies using the verbal and spatial chunking tasks described above have overcome this effect of task difficulty, demonstrating activation of PFC and PPC during the use of chunking strategies, despite reduced WM demand (Figure 1-3)^{24 26}.

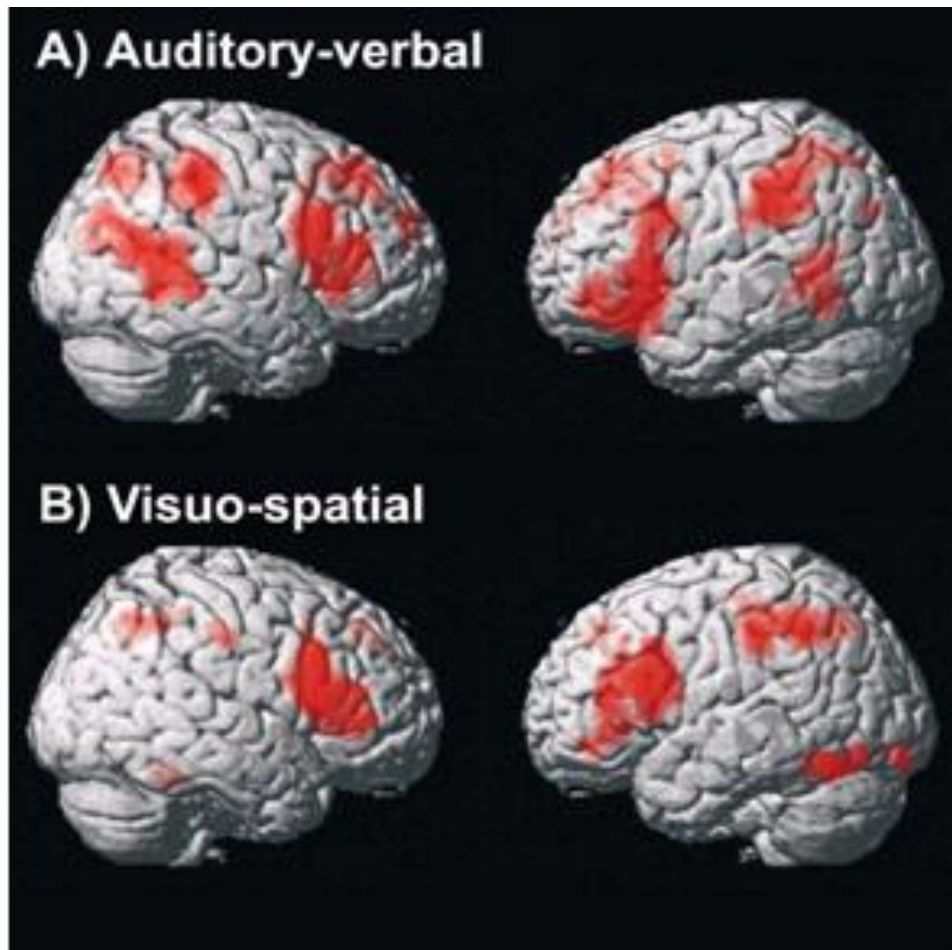


Figure 1-3 Common prefrontal and parietal activation patterns seen during chunking in verbal and visuospatial tasks. From Bor et al 2004²⁶

1.8 COGNITIVE TRAINING AND CHUNKING

Cognitive training involves the use of theoretically-driven strategies or exercises designed to target specific cognitive domains to optimise cognitive function⁴⁶.

Cognitive strategies used for training have been categorised as internal⁴⁷ (e.g. method of loci, association between modalities, or chunking), and external (using lists/diaries/alarms or pharmacological cognitive enhancers such as modafinil⁴⁸). Cognitive interventions for individuals with cognitive impairment have also been categorised according to whether the approach is restorative (i.e. seeking to strengthen and restore impaired function) or compensatory (i.e. seeking to work around impairments to improve function⁴⁹).

There have been inconsistent reports of the efficacy of cognitive training among healthy young subjects. Throughout childhood development and as adults, we learn new skills and develop expertise through practice and training. However, cognitive training appears to have limitations in

improving cognitive function in healthy adults. Physical exercise may build not only expertise in the specific sport trained but also lead to increased general levels of fitness, however it has been frustratingly difficult to demonstrate a similar effect with memory or other cognitive training. The evidence appears to be that cognitive training leads to improvements in the trained tasks but not an overall or generalised improvement in brain or cognitive 'fitness'. As an example, a recent large study demonstrated improvements in trained cognitive tasks but no transfer of benefits to untrained tasks⁵⁰. Despite this, a billion-dollar brain-training industry has developed offering software and tools that make various promises to improve brain function⁵¹.

There are however, a growing number of reports of cognitive training leading to generalised improvements to non-trained tasks, and WM has emerged as the focus of many of these approaches. A recent review of WM training in healthy subjects concluded that WM training may generalise to non-trained tasks that rely on WM and control of attention, consistent with training-induced plasticity in a common parietal-prefrontal network⁵². These improvements have also been associated with changes in PFC activity, and chunking has been postulated as a major strategy underlying these successful cognitive training regimes^{53 54}.

1.9 COGNITIVE TRAINING IN HEALTHY ELDERLY SUBJECTS

There is some evidence for the efficacy of cognitive training in healthy elderly subjects. In a large study, 2802 healthy elderly subjects demonstrated training-related improvements in memory and problem-solving⁵⁵, with benefits remaining at 5 year follow up⁵⁶, and some residual benefits at 10 year follow up⁵⁷. An earlier meta-analysis of 33 studies involving 1539 subjects also found a large effect size for episodic memory training in healthy elderly subjects⁵⁸.

1.10 PLASTICITY

The underlying neurobiological processes for changes seen at a cognitive level remain poorly understood. However plasticity at a cellular, synaptic and neural network level may underpin cognitive effects. There is growing evidence that plasticity persists throughout the age span and even in the context of neuro-degeneration⁵⁹⁻⁶¹. Therefore there is a theoretical basis for cognitive training having efficacy even in elderly subjects with early AD.

1.11 COGNITIVE TRAINING IN EARLY AD AND MCI

A recent systematic review of cognitive training in mild cognitive impairment (MCI)⁴⁶ described 7 studies of cognitive intervention. Of these, 6 reported improvement in objective measures of cognitive function following training. However it is still unclear as to whether cognitive training results in transferrable benefits or can reduce further deterioration in cognitive function in MCI.

The literature for cognitive training in AD demonstrates variable results and is limited by the relatively small number of RCTs, small sample sizes, a large variability in outcome measures, and multiple cognitive training techniques used, making it difficult to evaluate the efficacy of a single strategy. In order to identify whether there is evidence for cognitive interventions in AD a meta-analysis and meta-regression of the literature was performed and is presented in Chapter 2.

1.12 FUNCTIONAL IMAGING OF COGNITIVE TRAINING

There are a number of possible ways in which activation might change following training. Kelly and Garavan (2005), in a review of practice related changes in functional activity, identify three main patterns in the literature. Training may be associated with increased activation⁵³, or reduced activation⁶², due to increased neural efficiency. Alternatively functional reorganisation may occur with redistribution of activation within the existent neural network or function relocated to additional regions⁶³. Changes in functional connectivity both within and between neural networks is also hypothesised to be involved in training-related effects⁶⁴.

1.13 FUNCTIONAL IMAGING IN MCI AND EARLY AD

fMRI studies have demonstrated that when task-difficulty is controlled and only successful attempts at a cognitive task are examined, AD participants recruit similar brain regions to healthy controls⁶⁵. However, AD participants also show evidence of reduced functional connectivity between brain regions, including between PFC and PPC during WM tasks^{66 67}. Scanning participants pre- and post-cognitive training using identical tasks matched for performance allows cognitive improvement to be reflected in differential cortical activation. One study has used fMRI to examine healthy elderly controls and patients with MCI, before and after a cognitive training program primarily targeting episodic memory⁶¹. The MCI participants demonstrated training-related increased activation in a

large network of brain areas including frontal and parietal areas activated prior to training, and also the recruitment of alternative areas. This contrasted with the group of healthy elderly controls who demonstrated reduced activation after training in a similar network. An intriguing finding was that memory training normalized the initial brain activation deficits seen in MCI participants compared with controls. This study provides evidence for cognitive training-related plasticity in the early stage of neurodegenerative disease and supports the use of cognitive training. However, no study has yet investigated the effect of cognitive training on working memory in this way in early AD.

1.14 PILOT STUDY - CHUNKING IN EARLY AD

In a pilot study, the use of chunking strategies to improve WM performance was investigated in 13 participants with very mild AD (MMSE >23), 15 participants with mild AD (MMSE 18-23) and 15 healthy elderly controls⁶⁸. Verbal and spatial WM tasks were adapted from paradigms previously used in healthy young participants and briefly described above^{24 26}. In the verbal WM task, normal elderly controls and AD participants performed significantly better on structured compared to random trials, demonstrating successful use of chunking strategies to improve WM performance. In the spatial task, controls and participants with very mild AD performed significantly better on structured trials, however mild AD participants showed no significant span difference between the conditions. This was interpreted as a preserved ability to use chunking strategies to aid WM in early AD, which becomes lost by the mild-moderate stages of the disease (Figure 1-4).

This is in keeping with literature on executive dysfunction and WM in early AD, which suggests that strategic or executive WM tasks become impaired during mild-moderate AD, but are preserved at the earliest stages of the disease^{21 22 68}.

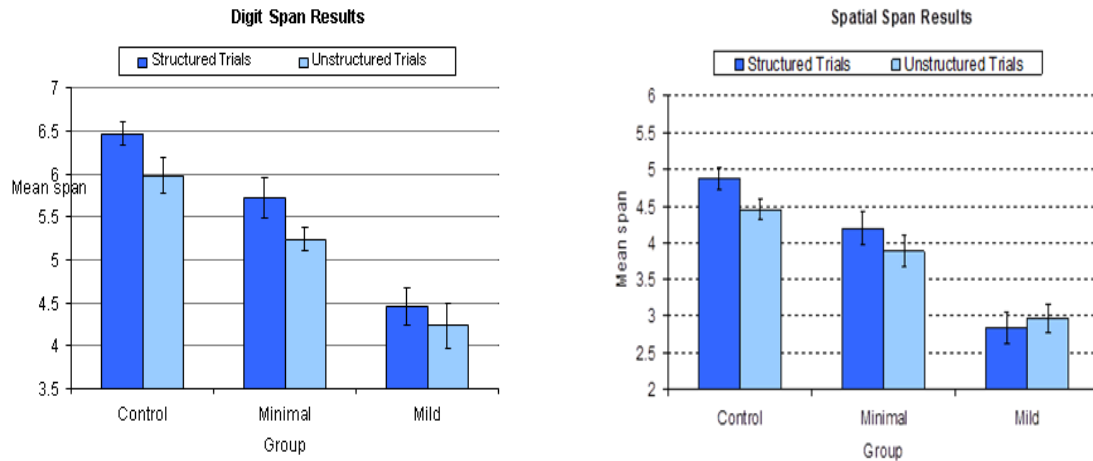


Figure 1-4: Digit and spatial span results from pilot study demonstrating improved performance with structured compared to random, unstructured trials⁶⁸.

1.15 IMPLICIT MEMORY AND COGNITIVE TRAINING IN AD

Declarative memory is assumed to be explicit and to depend on conscious awareness. Non-declarative or implicit memory, in contrast, is assumed to operate unconsciously and refers to memories whose recall is expressed through performance. Implicit memory has been demonstrated in complex cognitive tasks, such as learning rule structures in an artificial grammar task⁶⁹. A key observation made in the pilot study was that some control and early AD participants successfully benefitted from chunking strategies, despite not being explicitly aware of doing so. In a subset of early AD participants the hypothesis that explicitly informing participants of chunking techniques would improve WM performance in a single session was tested. This was indeed the case, suggesting that simple training in chunking techniques may lead to improvements in WM performance in early AD.

1.16 SUMMARY AND NEED FOR PROPOSED TRIAL

This current randomised controlled trial (RCT) combined theoretical insights into working memory and cognitive training, developments in functional neuroimaging in Alzheimer's disease and current knowledge of cognitive functioning within AD. There is an urgent need to further elucidate the effectiveness of cognitive training in early AD using theoretically - driven cognitive training regimes⁴⁹. The findings of preserved chunking ability in early AD provided a novel therapeutic target for effective cognitive training, and functional neuroimaging provides a powerful tool to demonstrate functional re-organisation as a result of cognitive training.

This randomised controlled trial investigated the impact of chunking training on WM capacity, general cognitive function and functional activity within PFC and PPC in early AD. My aim was that it would be novel, timely and would assess a simple intervention that may improve working memory capacity and preserve quality of life in the growing population of individuals with early AD.

Chapter 2 COGNITIVE INTERVENTIONS IN DEMENTIA - META-ANALYSIS AND META-REGRESSION

2.1 INTRODUCTION

Cognitive interventions for dementia, such as cognitive training (CT), cognitive stimulation (CS) and cognitive rehabilitation (CR) are widely used and NICE guidelines recommend the use of CS⁷⁰. However there is a lack of clarity over the efficacy and effectiveness of these interventions in terms of stabilisation or improvement in cognition, and a lack of information regarding individual cognitive outcomes. A Cochrane meta-analysis of CS included fifteen randomised controlled trials (RCTs) and concluded that CS significantly improved general cognitive outcomes such as the Mini Mental State Examination (MMSE⁷¹, mean difference = 1.74, 95% CI 1.13 to 2.36, $p < 0.001$) and Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog⁷², mean difference = 2.27, 95% CI 0.99 to 3.55, $p = 0.0005$)⁷³. A Cochrane review of twelve RCTs investigating CT or CR reported no significant improvements on any cognitive outcome measure⁷⁴. Neither of these meta-analyses examined the effects of including active or non-active control conditions on effect size.

By contrast, Sitzer et al (2006) reviewed 5 non RCTs and 12 RCTs of dementia cognitive interventions, defined by compensatory or restorative approaches. Overall effect sizes of 0.37 (SD: 0.45) for restorative and 0.40 (SD: 0.46) for compensatory interventions on general cognitive outcomes were reported⁴⁹, but studies that compared intervention to waiting list controls tended to produce greater effect sizes ($d = 0.53$, $SD = 0.47$) than those using attention-controlled placebo controls ($d = 0.36$, $SD = 0.58$, $p = 0.511$).

Most recently, Kurz et al (2011) found significant standardized mean differences (SMD) on the MMSE (SMD: 0.21, (95% CI 0.03, 0.39), $p = 0.02$) and ADAS-Cog⁷² (SMD: -0.3, (95% CI -0.48, -0.13), $p = 0.0005$) for CS, but not for CT and CR in a meta-analysis of RCTs in dementia and MCI. These authors concluded that there was no convincing evidence that these cognitive score changes generalised to any clinically significant improvements in quality of life or activities of daily living (ADLs)⁷⁵.

Consideration of these meta-analyses highlights the limitations of the evidence base. Methodological difficulties, such as a lack of suitable control interventions⁷⁶ and failure to maintain complete blinding to allocation, can mean that factors such as increased attention, socialisation or motivation could contribute to observed changes or that participant and investigator placebo effects may operate. This would be particularly expected for CS interventions which are often less specific in nature and encompass more social activities. A wide range of different approaches and cognitive outcomes are also used, which creates difficulties in comparing studies. The current analysis therefore had three aims.

Firstly it aimed to evaluate and compare the overall efficacy of each type of intervention (i.e. CT, CS or CR) on commonly-used clinical outcomes of general cognitive function (MMSE and ADAS-Cog), with consideration of the use of both active and non-active controls.

Secondly meta-regression analyses were conducted to examine associations between effect sizes and variables that may influence the efficacy of cognitive interventions.

Thirdly the efficacy of CT was investigated in more detail by examining outcome measures in specific cognitive domains.

2.2 METHODS

2.2.1 SELECTION OF STUDIES

Online literature databases and trial registers (Web of Knowledge, Cochrane Collaborative Central Register of Controlled Trials, PubMed/Medline) were searched using the terms in Figure 2-1. Previous meta-analyses and systematic reviews of cognitive interventions in dementia^{49 73-75 77} were also searched, in addition to leading journals.

INTERVENTION TERMS:	"cognitive stimulation" OR "cognitive rehabilitation" OR "cognitive training" OR "cognitive therapy" OR "cognitive retraining" OR "cognitive support" OR "cognitive intervention" OR "cognitive exercise" OR "cognitive strategy" OR "cognitive aid" OR "memory function" OR "memory rehabilitation" OR "memory therapy" OR "memory aid" OR "memory group" OR "memory training" OR "memory retraining" OR "memory support" OR "memory stimulation" OR "memory strategy" OR "memory management" OR "brain training" OR "brain rehabilitation" OR "brain stimulation" OR "brain retraining" OR "brain exercise" OR "neuropsychological training" OR "neuropsychological therapy" OR "neuropsychological strategy" OR "neuropsychological aid" OR "neuropsychological stimulation" OR "neuropsychological rehabilitation" OR "neuropsychological exercise" OR "neuropsychological intervention" OR "neuropsychological retraining" OR "neuropsychological support" OR "psychostimulation" OR "executive training" OR "executive stimulation" OR "executive rehabilitation" OR "attention training" OR "attentional training" OR "attentional rehabilitation" OR "global stimulation" OR "reality orientation"
STUDY TERMS:	RCT OR "controlled trial" OR random*
SUBJECT TERMS:	dement* OR "alzheimer's disease" OR alz* OR AD OR DAT OR DLB OR FTD OR VD OR "memory impairment" OR "cognitive impairment" OR "memory disorder" OR "cognitive disorder" OR "memory dysfunction" OR "cognitive dysfunction"

Figure 2-1: Search terms for systematic review

2.2.2 INCLUSION AND EXCLUSION CRITERIA

Studies were included in the meta-analysis if the study was a peer-reviewed RCT; participants had a diagnosis of dementia; mean age of participants in the study was greater than 60 years; sufficient data were available for calculation of effect sizes (unavailable information was requested from authors

and included if obtained); and the number of participants in each condition was more than 5 at any point,. RCTs were included if they compared a cognitive intervention to an active or non-active control or with another treatment (pharmacotherapy or other non-pharmacological therapy). An issue in assessing efficacy of cognitive interventions has been the description and classification of the intervention used. A useful approach is to divide these interventions into CT, CS and CR⁷⁷. Studies were screened and selected for inclusion and rated as to the best description of the intervention and control groups using the criteria described in Table 2-1. If it was decided that a study contained elements of more than one type of intervention it was classed as mixed e.g. mixed cognitive training and stimulation (MCTS). Active controls comprised of interventions that were designed to control for non-specific therapeutic effects, including time, attention and non-specific input from research or clinical teams (e.g. social support, psychoeducation, discussion groups, non-directed activities). Non-active controls consisted of treatment as usual (TAU), waiting list conditions, or a minimal intervention not matched for time, social interaction or with no specific cognitive content (Table 2-1).

COGNITIVE TRAINING	Repeated guided practice
	Uses standardised tasks
	Theoretically motivated strategies
	Range of difficulties (adaptive)
	Aims for improvement in isolated cognitive domain with possibility of generalization to non-trained tasks
COGNITIVE STIMULATION:	Wide range of activities
	Group format
	Significant emphasis on social interaction
	Aims for general improvement in cognitive function
	Non adaptive
COGNITIVE REHABILITATION:	Significant use of reality orientation or reminiscence therapy
	Individualised goals
	Aims to improve everyday function/ADLs
	Compensatory approach
ACTIVE CONTROL GROUP	Intervention matched for time/social interaction Intervention contains cognitive content not directly related to cognitive outcome measure.
NON-ACTIVE CONTROL GROUP	Waiting list/treatment as usual or minimal intervention not matched for time/social interaction/no specific cognitive content

Table 2-1: Definitions of cognitive interventions and control groups
Adapted from Clare et al⁷⁷

2.2.3 ASSESSMENT OF TRIAL QUALITY

A risk of bias tool⁷⁸ was used to assess study quality in five areas known to affect clinical outcomes (sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data and selective outcome reporting). Studies were rated as to the degree of bias in each study and if inadequate or unclear rates were scored in all five areas of bias the study was excluded from meta-analyses.

2.2.4 DATA EXTRACTION

Means and standard deviations (SD) or standard errors (SE) for each outcome measure in each condition and time point were extracted for each study. If means and SD were not available in published articles, authors were contacted and obtained information was included.

2.2.5 CALCULATION OF EFFECT SIZES

The methods for calculation of effect size, meta-analysis and meta-regression were based on recent meta-analyses by Gould et al^{76 79}.

For continuous data, effect sizes (g) were calculated by computing the mean change scores (Mpost – Mpre or Mfollowup – Mpre) between the intervention and comparator conditions (control or other treatment groups), which allows an estimate of effectiveness even when the intervention and control groups are non-equivalent. The mean change scores were divided by the pooled pre-intervention SD (SDpre) and corrected for upward bias (Cp) to account for bias resulting from small sample sizes and differences in degrees of freedom due to inclusion of pre-intervention means⁸⁰, (Equation 2-1).

$$g = Cp [(M_{post\ intervention} - M_{pre\ intervention}) - (M_{post\ comparator} - M_{pre\ comparator}) / SD_{pre}]$$

$$where\ SD_{pre} = \text{square root } [((N_{intervention}-1) SD_{preintervention}^2 + (N_{comparator}-1) SD_{precomparator}^2 / N_{intervention} + N_{comparator} - 2)]$$

$$and\ Cp = 1 - [3/4(N_{intervention} + N_{comparator} - 2) - 1]$$

Equation 2-1: Calculation of effect size (g)

If two or more comparisons from the same study were entered into the same meta-analysis, then the number of participants in the shared group was divided equally between comparisons to avoid double-counting participants.

If two or more outcomes within the same cognitive domain were reported within a single study a composite effect size was calculated. Composite scores were calculated by taking the mean of the effect sizes of the outcome measures within the same domain⁸¹, and calculating the variance of the mean of correlated outcomes (Y). (Equation 2-2).

$$V_Y = \left(\frac{1}{m}\right)^2 \times \left(\sum_{i=1}^m V_i + \sum_{i \neq j} (r_{ij} \sqrt{V_i} \times \sqrt{V_j}) \right)$$

Where m is the number of outcomes, V_i is the variance for several outcomes $i = 1, \dots, m$, and r_{ij} is the correlation between Y_i and Y_j ⁸¹

Equation 2-2: Calculation of the variance of correlated outcomes.

Domains were coded as memory, working memory, attention, executive function or other (incorporating language, visuospatial, speed of processing and praxis). All cognitive tasks are summarised with domain attribution in Table 2-4.

2.3 STATISTICAL ANALYSIS

2.3.1 META-ANALYSES

Random-effects meta-analyses using a DerSimonian and Laird estimator based on inverse variance weights were employed, as heterogeneity in treatment effects was anticipated because of between-study variations in clinical factors (e.g. content of intervention). Separate meta-analyses were conducted for subtype of cognitive intervention (CT, CS, CR and MCTS), in combination with subtype of control group (active or non-active) and outcome measure, to provide specific pooled effect sizes for each type of intervention and outcome. Separate meta-analyses were also conducted for each outcome measure at different time points (post-intervention [defined as 0-4 weeks after the intervention], 3, 6 and 9-12 month follow-up) to avoid non-independence of effect sizes.

For each meta-analysis, the overall effect size was calculated by weighing the average effect size for each study according to sample size and then pooling across studies. The z statistic was employed to test whether the pooled effect size was significantly different from 0. The I^2 statistic was used to examine variability in effect sizes between studies. The I^2 statistic estimates the proportion of variation in effect sizes due to heterogeneity, whereby values of 25%-49%, 50%-74% and >75% indicate low, moderate and high heterogeneity respectively⁸². High levels of heterogeneity in effect sizes between different studies can result in potentially misleading conclusions being drawn. If there was evidence of low to high heterogeneity, and greater than 3 studies were included in the meta-analysis, 95% prediction intervals were calculated in order to provide an estimate of the range of treatment effects within an individual study setting⁸³. Finally, publication bias was estimated using funnel plots and the Egger regression asymmetry test. If publication bias was detected, a non-parametric trim and fill method was used to impute missing studies and re-estimate the pooled effect size⁸⁴. An alpha level of 0.05 was used for tests of the estimated average treatment effect and publication bias. Data were analyzed using the metan function in Stata 10 (StataCorp, College Station, TX).

2.3.2 META-REGRESSION ANALYSES

Planned meta-regression analyses were used to examine whether any between-study heterogeneity could be explained by format of intervention (group or individual) and measures of study quality (sequence generation, allocation concealment, blinding of outcome assessors), as these have been suggested by previous analyses to influence effect size⁴⁹. Other variables examined were setting of intervention (outpatient/community vs inpatient/care home facilities), intensity of intervention (hours per week), length of intervention (weeks) and severity of dementia (as determined by mean MMSE score). If more than 30% of data were missing, the variable was excluded from analyses. The above variables, together with effect sizes, were entered into separate random-effects univariate meta-regression analyses using restricted maximum likelihood estimation. Knapp-Hartung adjustment was employed to control for risk of false positives with multiple covariates. Separate meta-regression analyses were conducted for the different general cognition outcome measures. Any factor that was significant in univariate analyses was entered into a random-effects multivariate meta-regression analysis that corrected for multiple comparisons (thus controlling for the risk of false positives). Data were analyzed using the metareg function in Stata 10.

2.3.3 CLINICAL SIGNIFICANCE AND SENSITIVITY ANALYSES

Mean change scores were also calculated as $(M_{\text{post intervention}} - M_{\text{pre intervention}}) - (M_{\text{post comparator}} - M_{\text{pre comparator}})$ to provide estimates for comparison with minimal clinically important differences (MCID) in general cognition outcome measures. For the ADAS-Cog, the most commonly cited measure, there is general agreement that a 4 point change is clinically significant⁸⁵. There is a greater range of opinion for the MMSE, with values of between 1.4^{86 87} and 3 being cited^{88 89}.

Sensitivity analyses were conducted by repeating random-effects meta-analyses of the main comparisons using SDs of mean change scores, without correction for upward bias, to calculate weighted mean difference scores. These weighted mean difference scores were then compared with the above definitions of MCID for the MMSE and ADAS-Cog.

2.4 RESULTS

The PRISMA checklist has been used to guide reporting of results⁹⁰. (Table 2-6).

Results are presented as:

- 1) Comparison of different cognitive intervention approaches using general cognition outcome measures, and meta-regression results.
- 2) Examination of specific cognitive domain outcomes in CT studies.

2.4.1 IDENTIFICATION AND CHARACTERISTICS OF INCLUDED STUDIES

Literature searches identified 2206 potential studies, 59 of which met inclusion criteria for data extraction. (PRISMA flow diagram Figure 2-2).

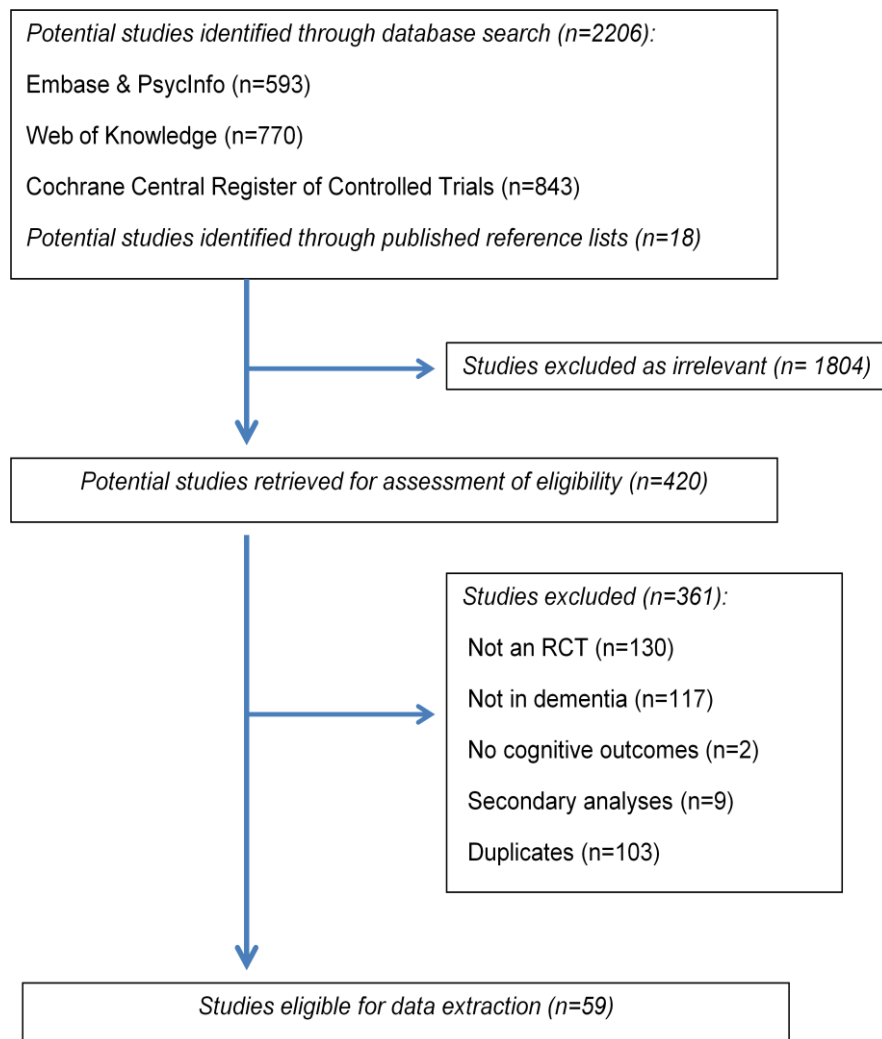


Figure 2-2: Flow diagram of inclusion of RCTs into meta-analysis

2.5 COMPARISON OF DIFFERENT COGNITIVE INTERVENTIONS

USING GENERAL COGNITION OUTCOMES

Of the 59 included studies, 33 contained general cognition outcome measures that could be included in meta-analyses⁹³⁻¹²⁵. Summary characteristics of these studies are presented in Table 2-7.

Four studies were classified as CT⁹¹⁻⁹⁴, 21 as CS⁹⁵⁻¹¹⁵, and 7 as mixed cognitive training and stimulation (MCTS)¹¹⁶⁻¹²². One study contained separate CS and MCTS interventions¹²³. There were no RCTs of CR with general cognitive outcomes.

Only 8 studies used active control groups^{91-93 99 100 116 117 121}. Twenty one studies used non-active control groups, whilst 2 studies had both active and non-active control groups^{114 122}. One study compared the intervention to other treatments and non-active controls¹⁰⁸, and 1 study compared the same intervention in different settings¹¹⁵.

The most commonly - used general cognitive outcome measure was the MMSE. Seventeen studies used the MMSE alone^{92-96 98-100 104 111 112 114 117-121}, 10 studies included both the MMSE and ADAS-Cog^{97 101 102 106 108-110 115 116 123} and 2 studies used the ADAS-Cog alone as a general cognition outcome measure^{103 105}. Two studies used only other general cognitive measures (CAS¹¹³ and MATTIS¹²²). Two studies used both the MMSE and one other general cognitive measure (MODA)^{91 107}.

Only 8 studies included follow-up data^{91 95 101 111 114 122 105 119}, ranging from 6 weeks to 10 months post-intervention, with the most common follow-up period being 6 months.

2.5.1 QUALITY OF STUDIES

Risk of bias and study quality is summarised in Table 2-8. Randomization was the least adequately addressed, with only 12 studies adequately or partially adequately reporting randomisation sequence and 10 studies adequately reporting allocation concealment.

2.5.2 META-ANALYSIS

Results of the meta-analyses conducted are presented in Table 2-2.

2.5.2.1 COGNITIVE STIMULATION

Post-intervention, there was a significant pooled effect size for CS vs non-active control on the MMSE ($g = 0.51$, (95% CI= 0.35, 0.66), $z = 6.23$, $p < 0.001$, Figure 2-3). There was low heterogeneity between studies ($I^2 = 24.9\%$). The calculated 95% prediction interval (0.124 to 0.89) suggested that the intervention was beneficial in individual settings.

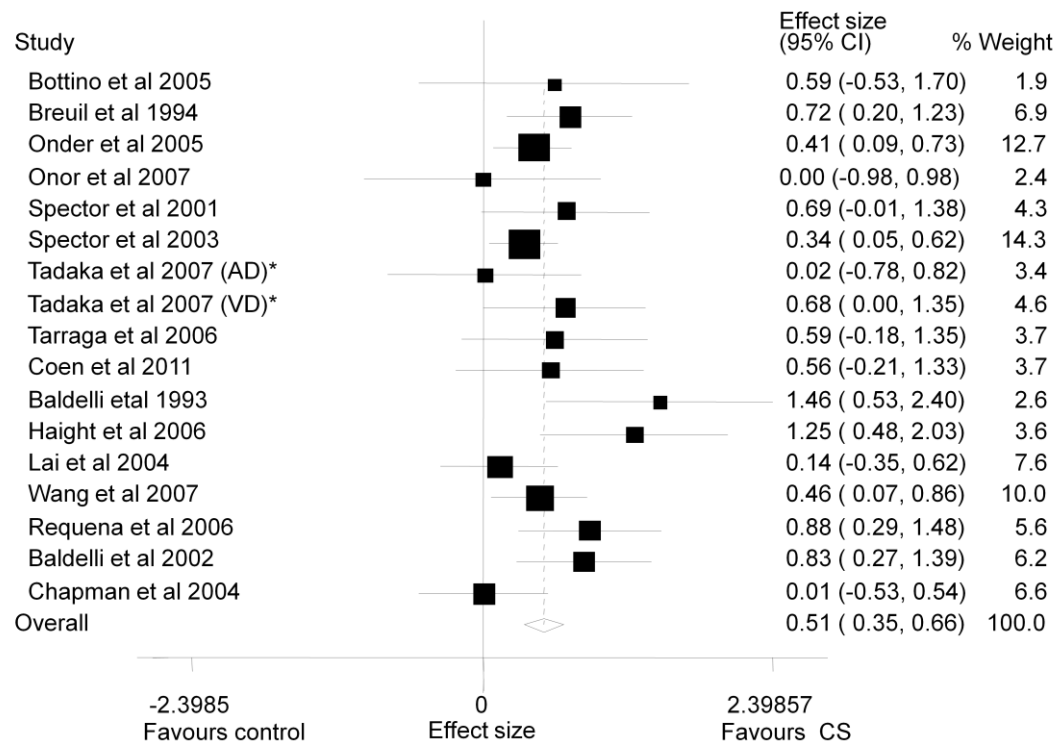


Figure 2-3: Forest plot of CS studies vs. non active controls: MMSE outcome

*Tadaka et al 2007 compared CS with control in two independent subgroups of Alzheimer's disease (AD) and Vascular dementia (VD) patients, therefore both could be included in same meta-analysis.

A smaller but still significant pooled effect size of 0.35 (95% CI 0.06, 0.64; $z = 2.34$, $p = 0.019$) was found for CS vs. active control on the MMSE (Figure 2-4), with no heterogeneity between the three studies ($I^2 = 0.0\%$).

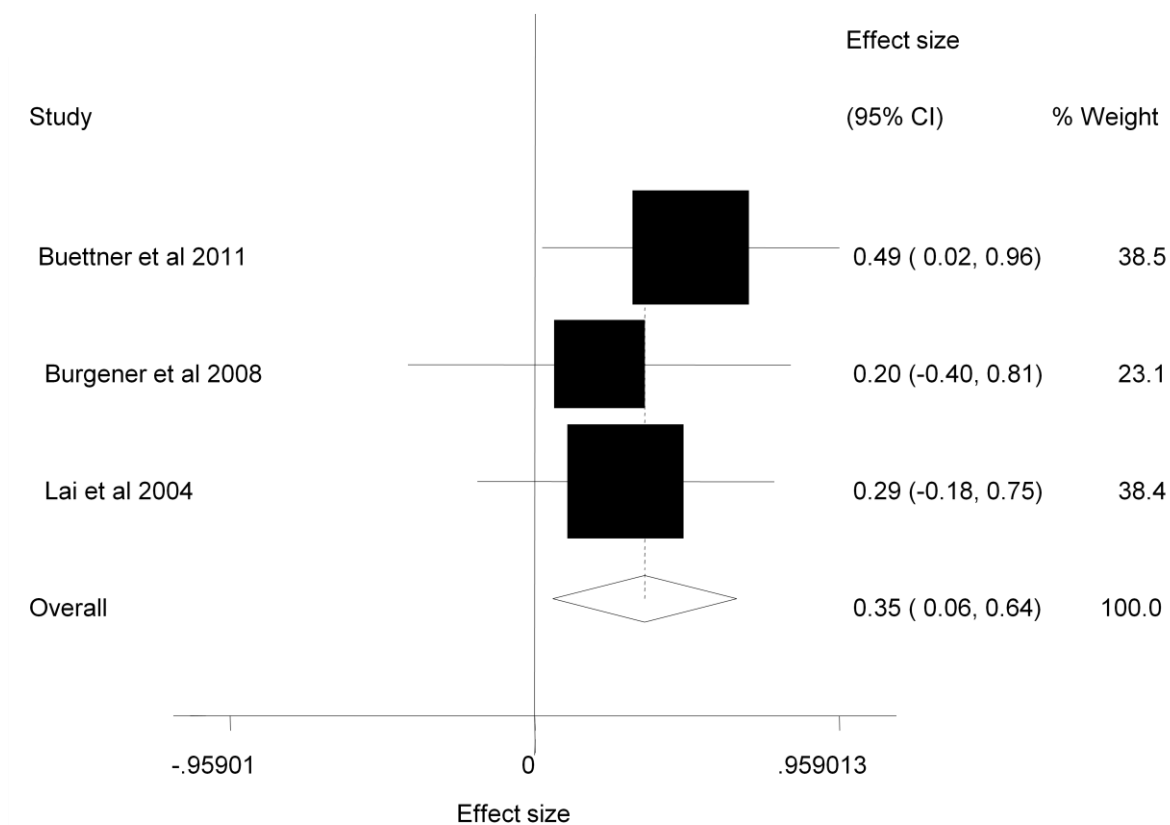


Figure 2-4: Forest plot of CS studies vs active control, MMSE outcome.

On the ADAS-Cog there was a significant pooled effect size favouring CS of -0.26 (95% CI -0.44, -0.08; $z = 2.82$, $p = 0.005$, Figure 2-5). There was low heterogeneity between the nine studies ($I^2 = 18.5$), however 95% prediction intervals (-0.62 to 0.10) suggested that the intervention may not be beneficial in individual settings. There were no studies comparing CS to active control that used the ADAS-Cog as an outcome measure.

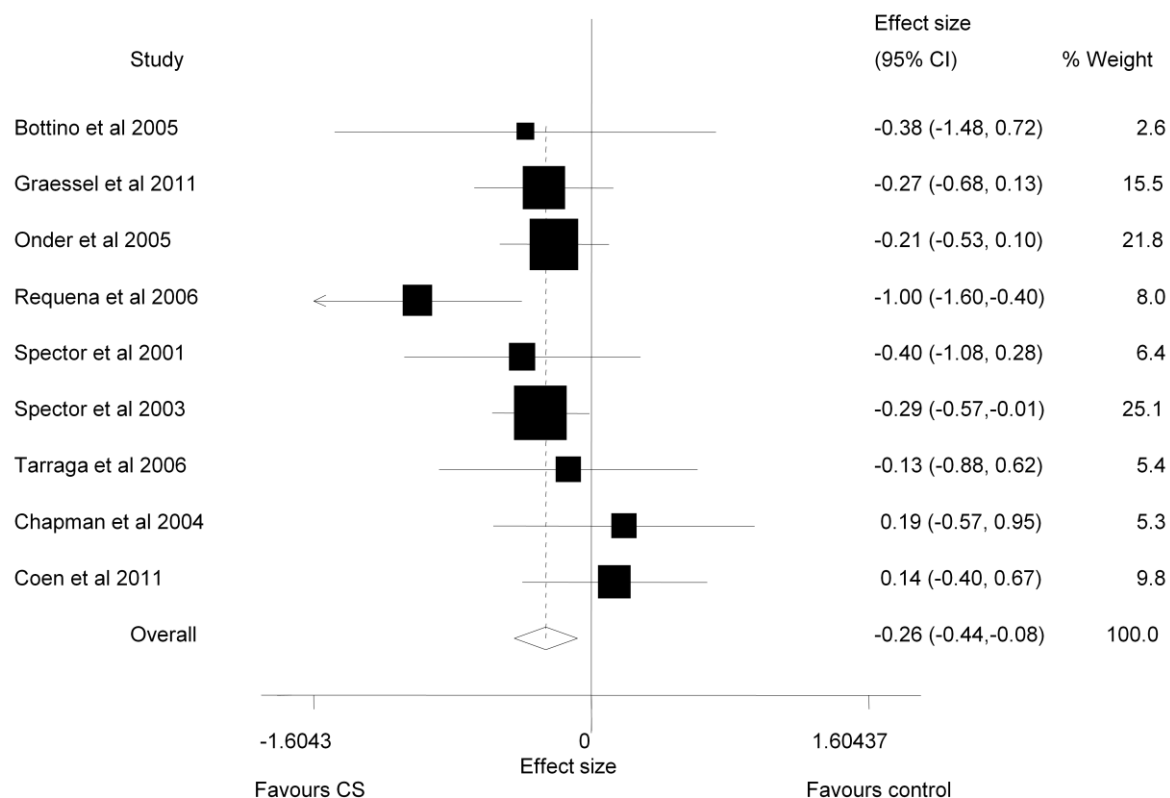


Figure 2-5: Forest plot of CS studies vs. non active controls, ADAS-Cog outcome.

Two CS vs. non-active control studies assessing other general cognitive outcome measures (CAS and MODA) were included in a meta-analysis. A non-significant positive effect size of 0.25 was found (95% CI -0.44, 0.94; $z = 0.71$, $p = 0.48$).

At up to 3 months follow-up, there was a pooled effect size of 0.796 in favour of CS (95% CI: 0.052, 1.539; $z = 2.10$, $p = 0.036$), on the MMSE, however both studies included in the analysis compared CS to non-active controls. There was moderate heterogeneity between these studies ($I^2 = 54.5\%$). By 6 months follow-up a non-significant pooled effect size of 0.273 (95% CI: -0.10, 0.64; $z = 1.45$, $p = 0.15$) was found on the MMSE, with no heterogeneity between the 3 studies ($I^2 = 0.0\%$). At 10 months follow-up, a significant effect of CS ($g = -0.40$ (95% CI: -0.723, -0.075); $z = 2.41$, $p = 0.016$) on the ADAS-Cog was seen.

2.5.2.2 COGNITIVE TRAINING

Only one study compared CT to a non-active control group⁹⁴, therefore no meta-analyses could be conducted. On the MMSE there was a non-significant pooled effect size of 0.22 favouring CT vs active controls (95% CI -0.745, 1.180; $z = 0.44$, $p = 0.658$). There was significant heterogeneity

between the three studies ($I^2 = 76.9\%$) and 95% prediction intervals (-11.033 to 11.467) suggested that the intervention may not be beneficial in individual settings.

There were no studies comparing CT to active or non-active control groups using the ADAS-Cog as an outcome measure. One study used the MODA as an outcome measure therefore no meta-analyses could be conducted.

2.5.2.3 MIXED COGNITIVE TRAINING AND COGNITIVE STIMULATION

Non-significant pooled effect sizes were found with MCTS vs. non-active, 0.447 (95% CI: -0.568, 1.462; $z = 0.86$, $p = 0.388$) and active controls, 0.253 (95% CI: -0.179, 0.686; $z = 1.15$, $p = 0.251$) on the MMSE. Heterogeneity between the three MCTS vs. non-active control studies was significant ($I^2 = 73.8\%$) with 95% prediction intervals (-11.333 to 12.227) suggesting the intervention may not be beneficial in individual settings.

It was not possible to conduct meta-analyses on studies comparing cognitive interventions to other treatments (e.g. pharmacological treatment) as only a single study investigated this¹⁰⁸. Similarly only a single study compared a cognitive intervention in different settings and therefore no meta-analysis was performed.

Analysis	No. of studies	N Tx/control	Pooled Effect size g (95% CI)	Overall effect: Z (P value)	Heterogeneity: I^2 % (P value)	Prediction interval: 95% CI	Publication Bias Egger's Test Bias coef (p)
Cognitive Stimulation							
Post-Intervention-MMSE CS vs NA CS vs Active	17 3	553/457 108/83	0.51 (0.35, 0.66) 0.35 (0.06, 0.64)	6.23 (<0.001) 2.34 (0.019)	24.9 (0.167) 0.0 (0.72)	0.12 to 0.89 N/A	1.09 (0.14) -2.67 (0.55)
Post-Intervention- ADAS-Cog CS vs NA <i>No studies of CS vs Active</i>	9	347/313	-0.26 (-0.44, -0.08)	2.82 (0.005)	18.5 (0.28)	-0.62 to 0.10	-0.017 (0.99)
Post-Intervention- Other general cog outcome CS vs NA	2	21/14	0.25 (-0.44, 0.94)	0.71 (0.48)	0.0 (0.75)	n/a	UC
Follow-up CS vs NA at 3 months (MMSE) CS vs NA at 6 months (MMSE) CS vs NA at 10 months (ADAS-Cog)	2 3 2	49/40 56/58 76/74	0.80 (0.05, 1.54) 0.27 (-0.10, 0.64) -0.40 (-0.72, -0.08)	2.10 (0.036) 1.45 (0.15) 2.41 (0.016)	54.5 (0.14) 0.0% (0.61) 0.0% (0.38)	n/a n/a n/a	UC -1.30 (0.76) UC
Cognitive Training							
Post-Intervention- MMSE CT vs NA CT vs Active <i>No studies of CT vs Active or Non-active using ADAS-Cog.</i> <i>No Follow-up studies of CT</i>	1 3	16/16 45/42	n/a 0.22 (0.75, 1.18)	n/a 0.44 (0.66)	n/a 76.9 (0.01)	n/a -11.03 to 11.47	UC -4.16 (0.61)
Mixed Cognitive Training and Stimulation							
Post-Intervention- MMSE CTCS vs NA CTCS vs Active	3 3	41/27 43/41	0.45 (-0.57, 1.46) 0.25 (-0.18, 0.69)	0.86 (0.39) 1.15 (0.25)	73.8 (0.02) 0.0 (0.39)	-11.33 to 12.23 N/A	-4.66 (0.79) 3.74 (0.22)

Table 2-2: Results of Meta-analyses of general cognitive measures

CS= Cognitive Stimulation, CT= Cognitive training, MCTS= mixed Cognitive training and cognitive stimulation interventions. NA= non-active control group, MMSE= Mini-Mental State Examination, ADAS-Cog= Alzheimer's Disease Assessment Scale-cognitive subscale, UC = unable to calculate;

2.5.3 META-REGRESSION ANALYSES

The results of the meta-regression analyses are presented in Table 2-3.

For both MMSE and ADAS-Cog outcome measures, meta-regression analyses revealed no significant associations between effect sizes and type of control group (active vs. non-active), setting (inpatient vs. outpatient), length of intervention, format of intervention (group vs. individual), intensity of intervention in hours per week, or mean severity of dementia of participants. In addition, there were no significant associations between effect sizes and measures of potential bias: randomisation sequence, randomisation allocation, blinding of outcome assessors, incompleteness of outcome data or selective outcome reporting.

The limited number of studies precluded meta-regression analysis at any of the follow-up time points.

Variables	Regression Coefficient (SE)	95% CI	P value	Q (P)	I ²
MMSE Outcome studies (n=30)					
<u>Continuous Variables</u>					
Length of intervention (weeks)	0.004 (0.003)	-0.002 to 0.010	0.244	38.3 (0.092)	0.270
Intensity of intervention (hours/week)	0.020 (0.019)	-0.018 to 0.059	0.287	38.2 (0.095)	0.267
Severity of dementia (mean MMSE)	0.010 (0.017)	-0.024 to 0.044	0.557	37.9 (0.062)	0.314
<u>Dichotomous Variables</u>					
Intervention (0= CS, 1= CT/MCTS)	-0.163 (0.152)	-0.461 to 0.135	0.284	38.7 (0.086)	0.276
Control (0= non-active, 1= active)	-0.163 (0.157)	-0.484 to 0.157	0.306	38.6 (0.088)	0.275
Setting (0=outpatient/community, 1= inpatient/care home)	0.153 (0.161)	-0.177 to 0.484	0.349	37.6 (0.065)	0.309
Format (0=group, 1=individual)	-0.233 (0.143)	-0.528 to 0.062	0.116	30.1 (0.147)	0.236
<u>Quality- related</u> (0=inadequate 1=adequate)					
Sequence generation	-0.070 (0.140)	-0.357 to 0.217	0.622	39.3 (0.075)	0.288
Allocation concealment	-0.155 (0.130)	-0.421 to 0.111	0.242	37.9 (0.101)	0.261
Blinding of outcome assessors	-0.184 (0.145)	-0.482 to 0.114	0.216	37.6 (0.105)	0.256
Incomplete outcome data	0.049 (0.150)	-0.257 to 0.356	0.745	39.6 (0.072)	0.293
Selective outcome reporting	-0.289 (0.325)	-0.954 to 0.376	0.381	38.6 (0.087)	0.275
ADAS-Cog Outcome studies (n=11)					
<u>Continuous Variables</u>					
Length of intervention (weeks)	-0.007 (0.003)	-0.014 to 0.0001	0.053	5.19 (0.818)	<0.001
Intensity of intervention (hours/week)	-0.007 (0.017)	-0.045 to 0.031	0.686	9.93 (0.356)	0.094
Severity of dementia (mean MMSE)	0.004 (0.025)	-0.052 to 0.061	0.860	8.63 (0.374)	0.073
<u>Dichotomous Variables</u>					
Intervention (0= CS, 1= CT/ MCTS)	-0.075 (0.381)	-0.937 to 0.788	0.849	10.08 (0.344)	0.107
Control (0=non-active, 1= active)	0.141 (0.554)	-1.112 to 1.394	0.805	10.05 (0.346)	0.105
Setting (0=outpatient/community, 1= inpatient/care home)	0.184 (0.311)	-0.552 to 0.920	0.573	9.67 (0.208)	0.276
Format (0=group, 1=individual)	0.061 (0.307)	-0.690 to 0.811	0.849	9.60 (0.143)	0.375
<u>Quality- related</u> (0=inadequate, 1= adequate)					
Sequence generation	0.239 (0.213)	-0.243 to 0.721	0.291	8.87 (0.450)	<0.001
Allocation concealment	0.239 (0.213)	-0.243 to 0.721	0.291	8.87 (0.450)	<0.001
Blinding of outcome assessors	0.408 (0.208)	-0.063 to 0.880	0.082	6.29 (0.711)	<0.001
Incomplete outcome data	0.270 (0.184)	-0.147 to 0.687	0.177	7.98 (0.536)	0.009
Selective outcome reporting	UC	UC	UC	UC	UC

Table 2-3: Results of meta-regression analyses. UC = unable to calculate;_Q= fit of model without heterogeneity|I²= proportion of variation due to heterogeneity

2.5.4 CLINICAL SIGNIFICANCE AND SENSITIVITY ANALYSES

Repeated random-effects meta-analyses of the main CS comparisons, using SDs of mean change scores, produced a significant weighted mean difference score of 1.78 (95% CI 1.23, 2.33; $p < 0.001$) for CS vs non-active control on the MMSE and -1.92 (95% CI: -3.43, -0.4; $p = 0.01$) for CS vs. non-active control on the ADAS-Cog. However the weighted mean difference score for the MMSE in CS vs. active studies was non-significant (1.45, 95% CI: -0.11, 3.02; $p = 0.07$).

Comparisons of the calculated mean change scores for each study were made with the range of published mean clinically important differences (MCIDs). For the CS studies, there was only evidence of the majority of studies (11/17) reaching minimal clinical significance with the lowest published threshold for MCID (1.4 MMSE points). However with the more conservative MCID of >2 MMSE points, only 9/17 CS vs. non-active studies and no CS vs. active control studies reached MCID. Of note, only 2/9 CS vs. non-active control studies reached MCID on the ADAS-Cog.

For the CT studies, the one study vs. non active controls met criteria for MCID of > 1.4 MMSE points. Of the CT studies vs. active controls, 2/3 did not meet criteria (i.e. mean difference < 1.4 MMSE points) however one study met criteria for MCID with a mean difference of > 2 MMSE points. Out of the 6 MCTS studies with MMSE outcomes, 2/3 of the MCTS vs. active and 2/3 of the MCTS vs. non active controls did not meet criteria as mean difference < 1.4 MMSE points, and 1/3 of studies for each type of control group met criteria for mean difference > 1.4 but less than 2. Of the 2 MCST studies with the ADAS cog as an outcome, neither met MCID.

2.6 EXAMINATION OF SPECIFIC COGNITIVE OUTCOMES IN CT AND MCTS STUDIES.

Tasks were classed according to which cognitive function they primarily assessed. The cognitive domains were divided into working memory (WM), episodic memory (MEM), attention (ATT), executive function (EXEC), or 'other' (incorporating language, visuospatial function, speed of processing and praxis). Cognitive tasks that were included in the meta-analyses and their domain are summarised in Table 2-4.

Out of the 59 studies, 9 CT studies^{91-94 124-128} and 6 MCTS studies^{116-120 123} had data on specific outcome domains that could be included in meta-analysis. All outcome measures used in each study with their calculated effect sizes are shown in Table 2-5. Due to the limited number of studies that contained comparable outcomes, studies with active and non-active controls were combined in single meta-analyses to examine overall effects within cognitive domains. Composite effect size values were calculated for episodic memory outcomes in four CT studies^{92 93 125 127} and three MCTS studies^{117 118 128}. Composite effect size values were also calculated for executive function outcomes in four CT studies^{91 93 94 126} and four MCTS studies^{116 117 119 128}. No studies contained data on correlations between outcomes within cognitive domains. Therefore composite values were calculated using a plausible correlation between tasks of $r = 0.5$, based on previous studies^{81 129}.

TASK	DOMAIN	BRIEF DESCRIPTION	STUDY USED
Corsi block tapping test ¹³⁰	WM	Grid of blocks is presented and a number are tapped sequentially. Subjects asked to recall the order the blocks were tapped. (+ve scored)	Galante (2007) Heiss (1994)
Digit span ¹³¹	WM	Sequence of digits is read aloud. Subjects asked to immediately recall digits in the correct order. If correct, a sequence with an additional digit is presented. (+ve scored)	Jelcic (2012) Beck (1988)
Dual task ¹²⁶	EXEC/WM	Two arithmetic tests of different levels of difficulty- a 2 step forward calculation, and a 3 step backward calculation. Cog performance was measured as the number of correct calculations. Also used to measure a Dual task cost in percentage when combined with timed walking test. (dual task –ve scored)	Schwenk (2010)
Recog and recall memory tasks ¹²⁷	MEMORY	Four tests used, (+ve scored) subjects asked to learn and recall: 1)15 item list of semantically unrelated words, 2)paired associates task (six word pairs of low probability of being commonly associated) 3)familiar pairs task (6 word pairs that are commonly associated) 4)list of 6 familiar daily tasks that can be readily grouped into categories.	Zarit (1982)
Object recall ¹²⁵	MEMORY	A tray with 15 categorisable everyday objects is shown for 1 minute. Total number of objects recalled by subject and carer together (collaborative recall) and individually (individual) is scored. A 'clustered' version also performed, where the objects were arranged in category clusters on the tray. (+ve scored)	Neely (2009)
Word recall ¹³²	MEMORY	12 nouns read one at a time. Task is to remember as many words as possible for immediate recall. Categorisable and non categorisable words are presented (+ve scored)	Neely (2009)
Brief story recall ⁹³	MEMORY	Subjects asked to recall short story (+ve scored)	Jelcic (2012)
Rey-osterrieth complex figure ¹³³	MEMORY	Subjects shown complex figure and then tested on their delayed recall of the figure (+ve scored)	Jelcic (2012)
Rey auditory verbal learning test ¹³⁴	MEMORY	A list of 15 words is read aloud. Subject repeats all the words he/she can recall. This procedure carried out 5 times. Another list of 15 words is then presented, with one attempt at recall. Immediately following this, subjects asked to remember as many words as possible from the first list. (+ve scored)	Jelcic (2012)
Delayed recognition task ⁹²	MEMORY	Series of words and pictures were presented. Subjects then asked to recall these and Scored on 'verbal reminding' , and Recognition (hits) (+ve scored)	Heiss (1994)

Gollin incomplete picture test ⁹²	MEMORY	Subjects are shown a series of fragmented pictures in a sequence, from most to least fragmented, and asked to identify the image .Task administered on 2 occasions. (+ve scored)	Heiss (1994)
Hopkins verbal learning test-revised ¹³⁵	MEMORY	12 nouns (4 words each from 3 semantic categories) are learned over 3 trials. 25 min later, a delayed recall trial (free recall) and a recognition trial (12 target and 12 false words) are completed. (+ve scored)	Cahn Weiner (2003)
Brief visual spatial memory test-revised ¹³⁶	MEMORY	6 figures, arranged in a 2 X 3 matrix are displayed for 10s. 4 tests attempted: 1)immediate recall 2)additional 10s exposures, followed by recall successive trials. 3)delay recall of figures (25 minutes later without any further exposure) 4)recognition trial (all +ve scored)	Cahn Weiner (2003)
Controlled oral word association test /fluency ¹³⁷	EXEC	Asked to orally generate words beginning with F, A, S in 1-min periods. The total score is the sum of the number of words generated across the 3 trials alternate version asks subjects to generate nouns within a category(+ve scored)	Cahn Weiner (2003) Galante (2007) Heiss (1994) Jelcic (2012))
Trail making test ¹³⁸	EXEC	Part A subject connects 25 encircled numbers in order. Part B subject connects 25 encircled letters and numbers in alternating, ascending order. Performance is timed on both parts- less time= less impaired	Cahn Weiner (2003) Jelcic (2012)
Ravens progressive matrices ¹³⁹	EXEC/IQ	60 patterns present in order of difficulty. Subjects asked to identify the missing element that completes a pattern (+ve scored)	Galante (2007)
Stroop test ¹³⁷	EXEC	Written colours differ from the ink colour they are printed in. Subjects have to first say the written word, and in the second trial name the ink colour instead (timed- -ve scored)	Jelcic (2012)
Frontal assessment battery ¹⁴⁰	EXEC	Battery of simple bedside tests of sequencing, behavioural inhibition (go no go), motor sequencing and frontal release signs (+ve scored)	Kawashima (2005) Maci (2012)
Digit cancellation test ¹⁴¹	ATT	Subjects asked to cross out specific digits from a list of numbers. Score consists of the correctly crossed out numbers minus the incorrectly crossed out numbers (+ve scored). Letter cancellation version used by Beck et al. Attention and Concentration task used by Heiss- details unclear.	Jelcic (2012) Galante (2007) Beck (1998) Heiss (1994)

Table 2-4: Brief description of specific cognitive tasks. reported in studies included in the meta-analyses
WM = working memory, MEMORY = episodic memory, EXEC = executive function, ATT = attention.

STUDY	WM	G	EM TASK	G	EXEC TASK	G	OTHER TASK	G
HEISS 1994 Computerised MDT AC	SS	-0.40	VER REMIND	0.23	FLUENCY	0.64	TOKEN TEST(LANG)	-0.17
			RECOG HITS	0.37			ORIENTATION	0.29
			RECOG FALSE POS	-0.12			ATT	0.48
			FRAG PIC DIFF	0.10			PRAXIS	-0.45
			1ST PRES	0.19			REACTION TIME	0.08
			2ND PRES	0.14			PROCESSING SPEED	0.33
GALANTE 2007 Computerised MDT AC	SS	-0.33	WORD REP	0.14	FLUENCY (C)	-0.02	MATRICES (IQ)	-0.04
			PROSE MEM	-0.14	FLUENCY (C)	0.56	DIGIT CANC (ATT)	-0.34
							DENOMINATION	-0.17
							CONST APRAXIA	-0.11
							IDEO APRAXIA R	0.42
							IDEO APRAXIA L	0.02
JELCIC 2012 Focused lexical semantic training AC	DS	0.65*	RECALL- IMM	0.31	FLUENCY (L)	0.03	REY FIG COPY	0.25
			RECALL- DEL	0.61	FLUENCY (C)	0.06	CLOCK DRAWING	-0.08
			RECALL- RAVL DEL	0.72*	STROOP	-0.23	BNT	0.51
			REY FIGURE	0.00	TRAIL A	-0.32	verbal NT (SM)	0.79*
					MATRICES (IQ)	-0.08		
NEELY 2009 Taught: -spaced retrieval ----hierarchical cueing - face name recall and IADL -Either individual (IND) or with carer (COL) NAC			RECALL object rand- COL	1.70*				
			RECALL object clust- COL	0.96*				
			RECALL rand word- COL	0.40				
			RECALL word cat- COL	0.60				
			RECALL object rand- IND	0.24				
			RECALL object clust- IND	0.27				
			RECALL rand word- IND	0.30				
			RECALL word cat- IND	0.00				
ZARIT 1982 Taught Association (word-image) NAC			RECALL daily task	-0.43				
			RECALL unrelated words	1.11*				
			RECALL unfamiliar	1.15*				

			words					
			RECALL familiar words	0.27				
			RECOG daily task	-0.01				
			RECOG unrelated words	0.03				
			RECOG unfamiliar words	0.02				
			RECOG familiar words	0.31				
SCHWENK 2010 Dual task training AC	DTC 2	0.11			DTC serial 3 back	0.49		
					DTC combine 3	0.82*		
					DTC combine 2 (EX + WM)	0.25		
KAWASHIMA 2005 Arithmetic and reading aloud NAC					SIMILARITIES	0.93*		
					FLUENCY	0.12		
					MOTOR PROG	0.68		
					CONFLICT INST	0.18		
					GO NO GO	-0.23		
					PREHENSION	N/D		
MACI 2012 physical exercise and MDT NAC					FAB	0.78		
CAHN WEINER 2003 Taught: -categorization -visualisation -association AC			HVLT TOTAL	0.27	COWA	-0.11	JLO (PERC)	-0.50
			HVLT RECALL	0.24	TRAILS A	-0.48	BNT (SM)	0.07
			HVLT RECOG	0.26	TRAILS B	0.32		
			BVSMT TOTAL	-0.48				
			BVSMT RECALL	-0.13				
			BVSMT RECOG	0.26				
TARRAGA 2006 Computerised MDT+ stimulation and IADL training AC + NAC					FLUENCY (SEM)	-0.43	BNT (SM)	-0.03
			SKT	-0.22	FLUENCY (P)	-0.09		
BECK 1988 Focus on attention and reading, used object matching, concentrating on detail in adaptive training. adaptive. NAC			DIGIT RECALL	0.75			ATTENTION/READ	-0.60
			VERBAL RECALL	0.09			MATCH (PERCEP)	-0.32
							CONC (DIFF ORIENT)	-0.23
DAVIS 2001 Spaced retrieval , association (number-object) taught	DS	-0.25	RECALL IM (LM1)	0.30	VSAT SECS (EX ATT)	-0.21		
	DS	0.22	RECALL DEL	-0.16	VSAT ERR (EX ATT)	0		

AC	BACK							
			VISUAL REP	-0.20	COWA	-0.09		
			VISUAL REP DEL	0.33	FLUENCY	0.08		
					FLUENCY	0.17		
KOLTAI 2001 spaced retrieval Face-name recall verbal elaboration, repetition, external aids, coping strategies NAC			WLM TOTAL	-0.45				
			WLM RECALL	0.58				
KURZ 2012 external aids establishing routines reminiscence planning NAC			WMS LM	0.01	TRAILS A	0.14		
					RWT	-0.12		
BUSCHERT 2011 visual imagery face-name association external memory aids reminiscence Multisensory Stimulation errorless learning approach AC			RBANS RECALL	0.43	TRAILS A	0.01		
					TRAILS B (EX)	-0.88		

Table 2-5: All cognitive outcomes and calculated effect sizes (Hedges g) for CT and MCTS studies

*Significant effect sizes are in red. AC= active control. NAC= non active control. WM = working memory, EM= episodic memory, EXEC = executive function, LANG = language, PERC= perception, ATT= attention. MDT= Multi domain training (i.e. several tasks training different cognitive domains), SS = spatial span, DS = digit span. See Table 2-4 for description of tasks.

2.6.1 COGNITIVE TRAINING STUDIES- EPISODIC MEMORY OUTCOMES

Meta-analysis of all CT studies with episodic memory outcomes revealed a significant pooled effect size of 0.34 ((95% CI 0.014, 0.672), $z = 2.04$ $p = 0.041$) with no heterogeneity between studies ($I^2 = 0.0\%$),(Figure 2-6)

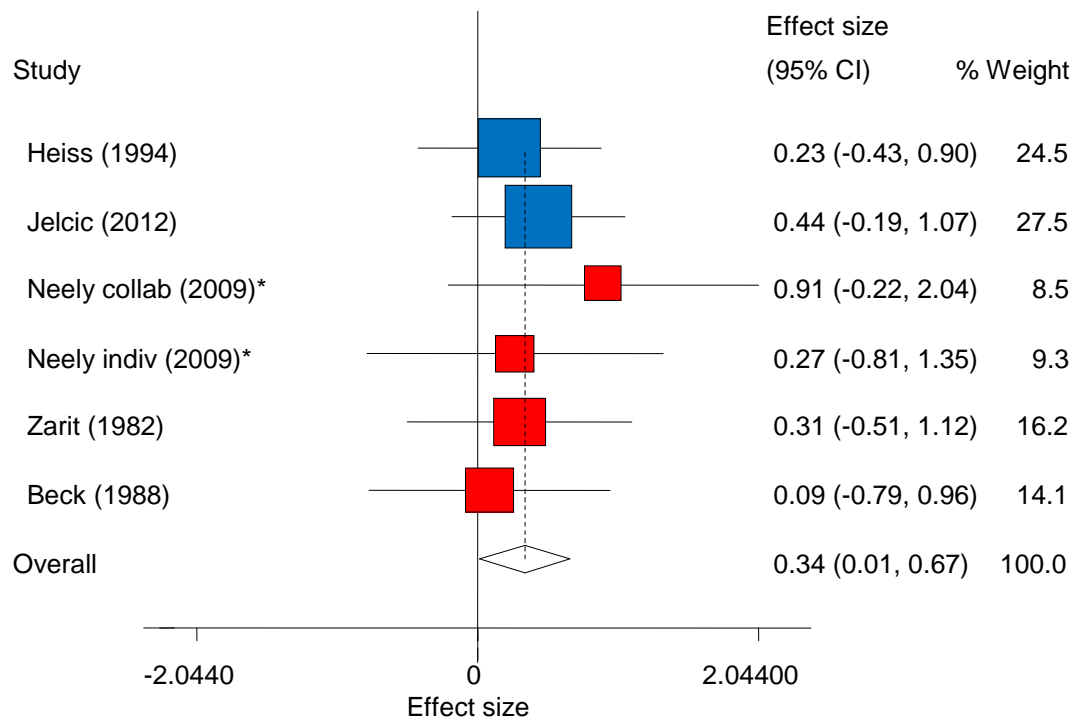


Figure 2-6: Forest Plot of CT studies with memory outcome measures. Blue= active controls, Red = NA controls. *Neely (2009): number of controls corrected for inclusion of 2 independent experimental groups in same meta-analysis

2.6.2 COGNITIVE TRAINING STUDIES – EXECUTIVE FUNCTION OUTCOMES

Meta-analysis of CT studies with executive function outcomes produced a significant pooled effect size of 0.40 ((95% CI: 0.11, 0.70), $z = 2.66$ $p = 0.008$), with no heterogeneity between studies ($I^2 = 0.0\%$). (Figure 2-7).

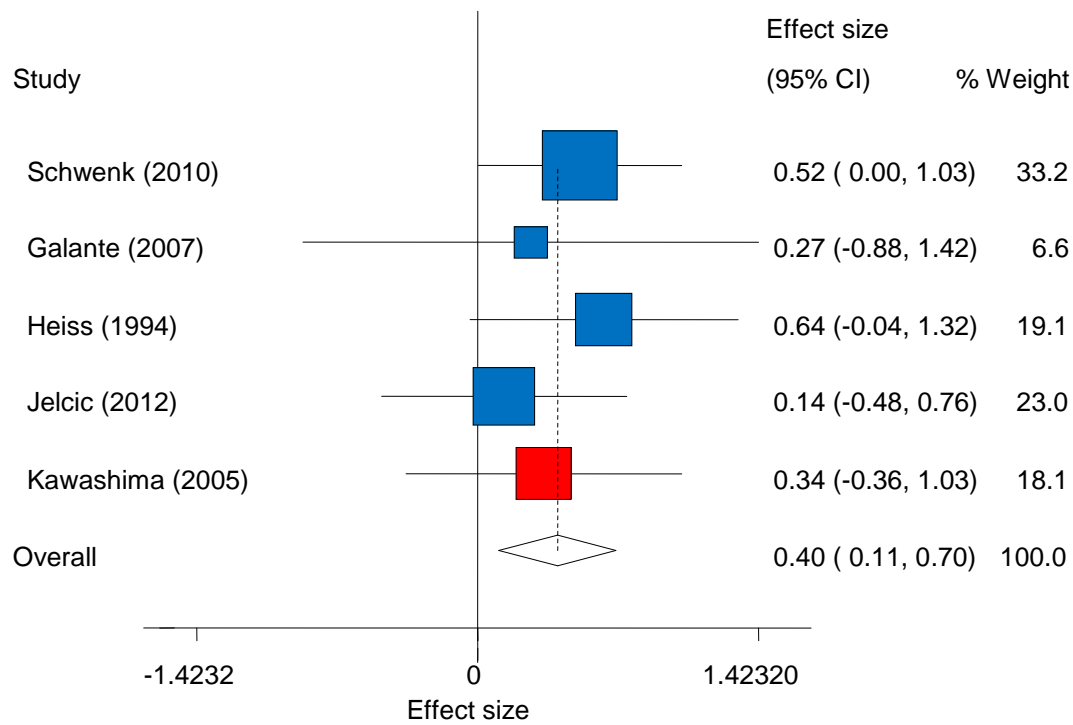


Figure 2-7: Forest plot of CT studies with executive function outcomes.
Blue= active controls, Red = NA controls

2.6.3 COGNITIVE TRAINING STUDIES- WORKING MEMORY OUTCOMES

Figure 2-8 shows the forest plot of 5 CT studies with working memory outcomes. 4 used active controls and 1 used NA controls. The pooled effect size was non significant (0.17 (95% CI: -0.27, 0.61), $z = 0.77$, $p = 0.444$) with moderate heterogeneity between studies ($I^2 = 45.6\%$).

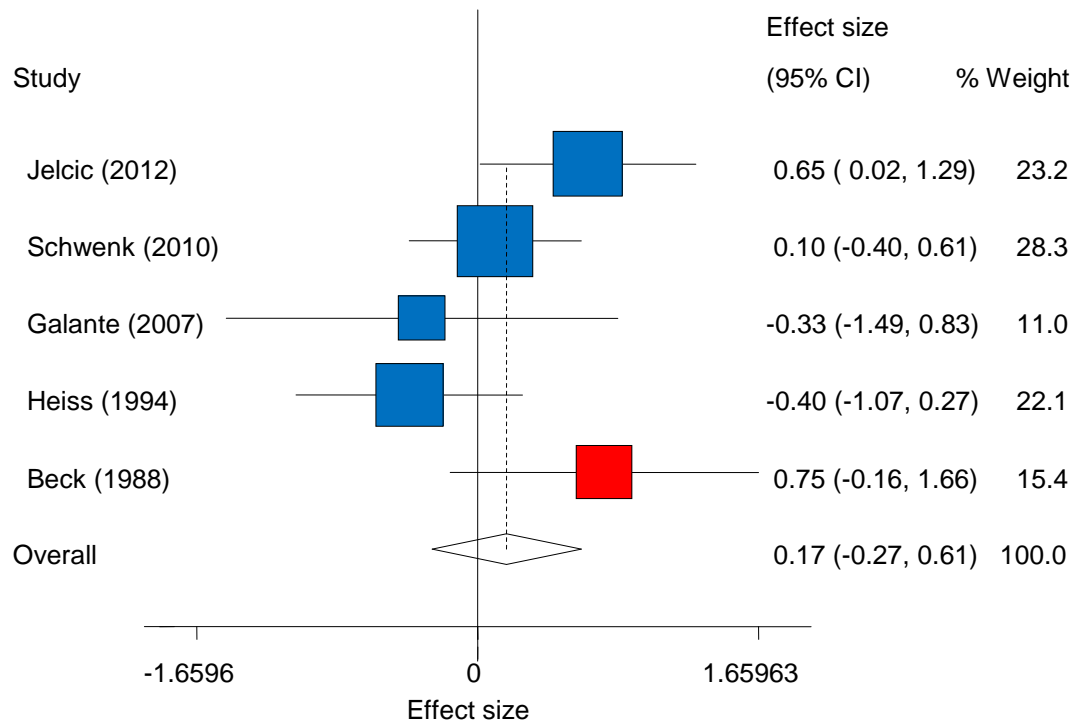


Figure 2-8: Forest plot of CT studies with working memory outcomes. Blue= active and Red= non active control groups.

2.6.4 COGNITIVE TRAINING AND ATTENTION OUTCOME MEASURES

4 studies included outcome measures of attention. The pooled ES was non significant (-0.05 (95% CI : -0.51,0.41) $z = 0.22$, $p = 0.829$), with low heterogeneity between studies ($I^2 = 26.2\%$). (

Figure 2-9).

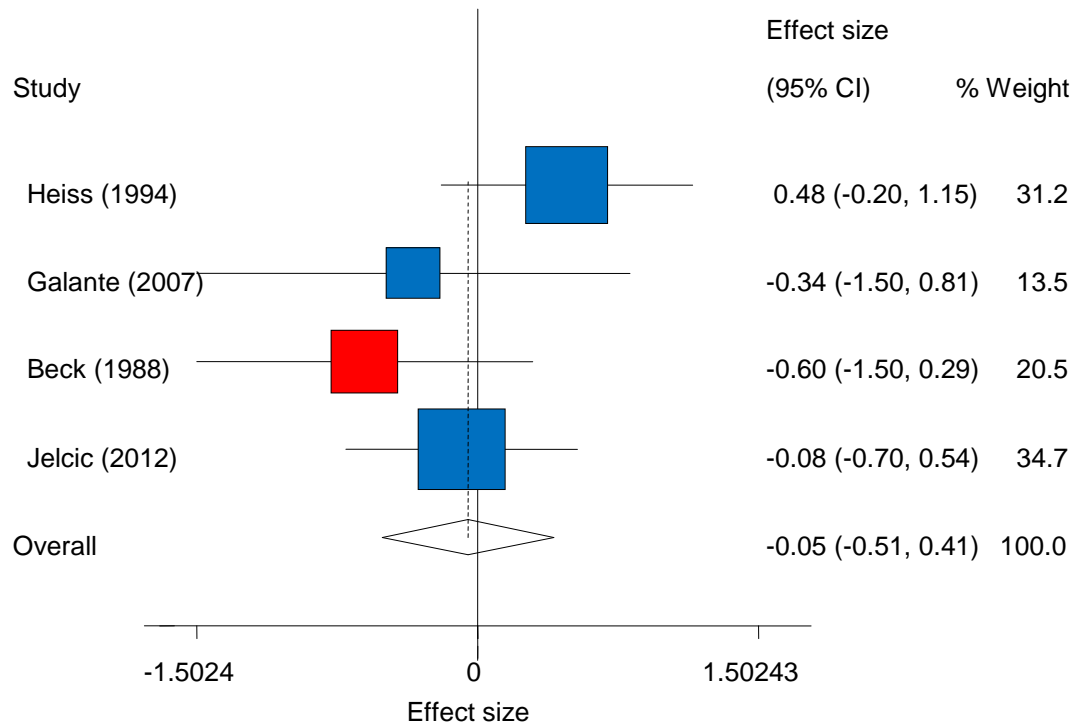


Figure 2-9: Forest plot of cognitive training studies and attention outcome measures
Blue= active controls, red = non active controls.

There were not enough comparable outcome measures of other cognitive domains to enter into a meta-analysis. Effect sizes for individual outcome measures are listed in Table 2-5.

2.6.5 MCTS STUDIES- EPISODIC MEMORY OUTCOMES

Three studies used active controls and 3 studies used non active controls. Combining all studies in one meta-analysis revealed an overall non-significant pooled ES of 0.02 ((95% CI -0.19, 0.24), $z = 0.20$ $p = 0.838$), with no heterogeneity between studies (Figure 2-10).

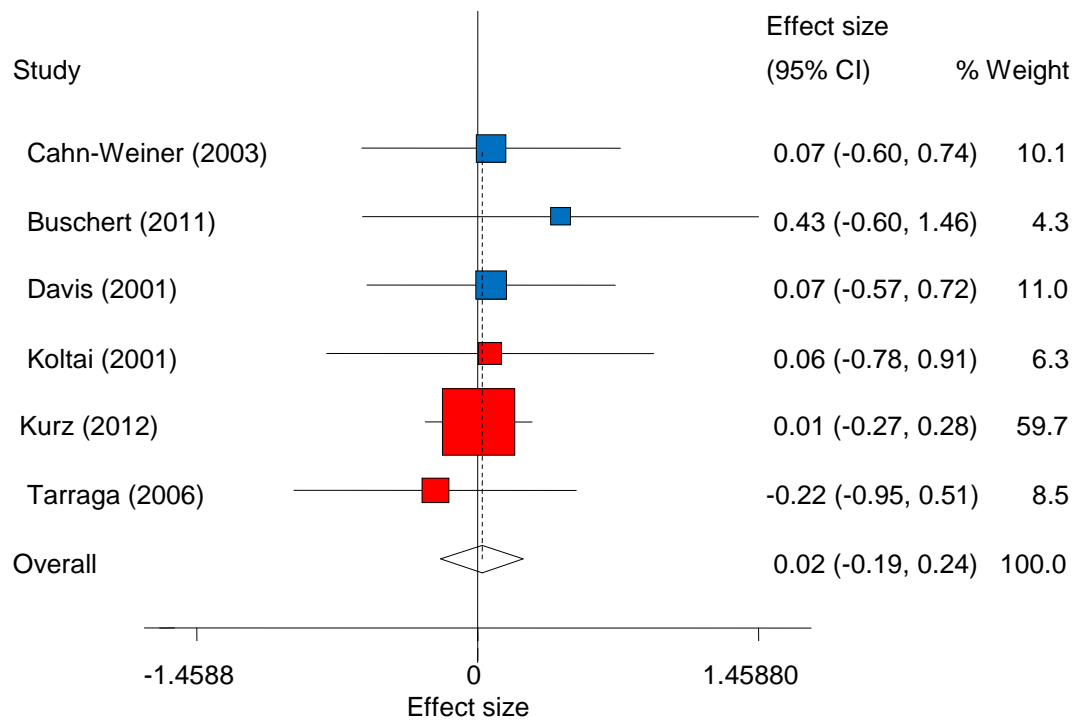


Figure 2-10: Forest Plot of MCTS studies with memory outcome measures. Blue= active control groups and Red = non active controls

2.6.6 MCTS STUDIES WITH EXECUTIVE FUNCTION OUTCOMES

Three studies with active control groups and two studies with non active control groups included executive function measures. Combining all studies, the ES was non-significant ($g = -0.03$ (95% CI: -0.25, 0.20), $z = 0.23$, $p = 0.815$) with no heterogeneity between studies (Figure 2-11).

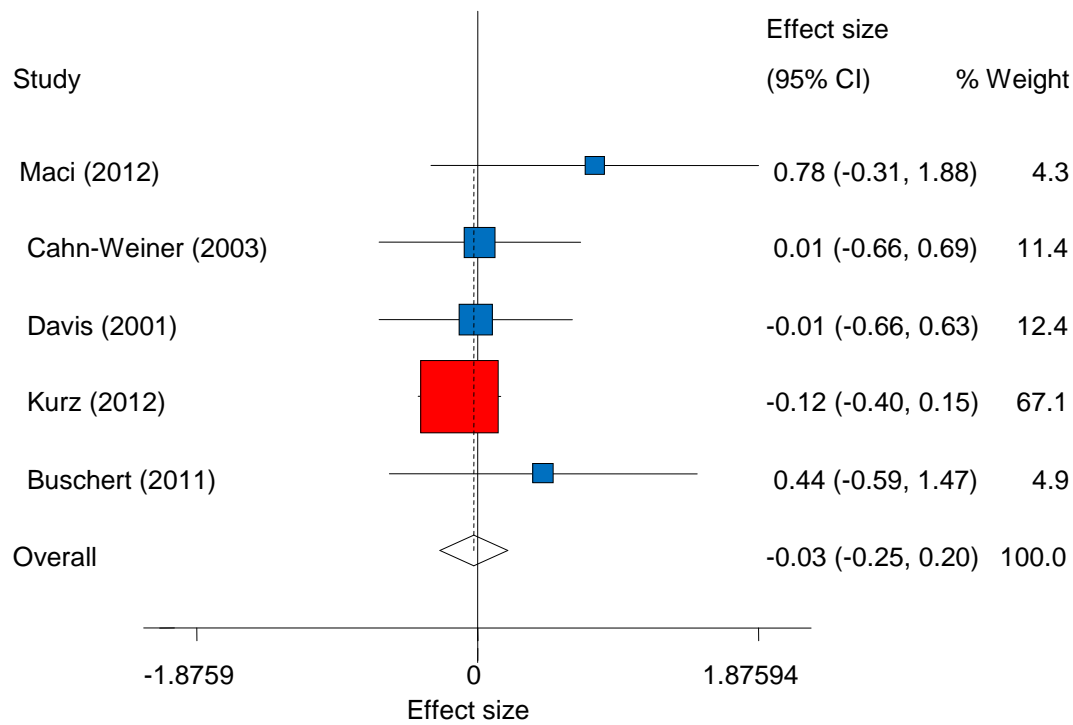


Figure 2-11: Forest Plot of MCTS studies with executive function outcomes. Blue = active controls, Red = non active controls.

2.7 DISCUSSION

2.7.1 GENERAL COGNITIVE FUNCTION

There was evidence of statistically significant efficacy of CS when MMSE was used as the outcome measure, although effect sizes were small to moderate in magnitude (0.35 for active and 0.51 for non-active controls). ADAS-Cog score also showed significant improvement in comparisons with only non-active controls, again with a small effect size of -0.26. Where there was heterogeneity between the trials reviewed, prediction intervals indicated that CS was beneficial in individual settings as measured by the MMSE but not the ADAS-Cog. The meta-analyses results are consistent with recent Cochrane reviews in finding little evidence for significant efficacy of CT in dementia, however there were fewer CT trials that included general cognitive outcome measures. Interventions using a mixture of CT and CS approaches also did not significantly improve general cognition.

Examination of between-group mean MMSE difference scores revealed that only when the lowest threshold for the MCID are used did the majority of CS studies (13/20 studies) reach minimal clinical improvement. The weighted mean difference for CS studies compared to adequate active controls of 1.45 (95% CI -0.11, 3.02; $p = 0.07$) only just reached the lowest MCID threshold of 1.4 points, and was not statistically significant in the sensitivity analysis. When the ADAS-Cog was used as an outcome measure, only 2 out of 9 studies versus non-active controls (and no studies versus active controls) demonstrated mean differences of greater than 4 points, and the weighted mean difference for all studies of -1.92 (-3.43 to -0.4) lies well below the MCID of 4. Due to this limited evidence of clinically important differences in MMSE or ADAS-Cog scores when interventions are compared to an adequate placebo control, although statistically significant improvements in MMSE or ADAS-Cog scores are seen with CS, this analysis is consistent with that of Kurz et al⁷⁵ in finding that there is currently only limited evidence that any cognitive intervention leads to clinically significant general cognitive improvement in dementia.

A significant issue here is the inadequacy of blinding and placebo controls in psychosocial RCTs such as those of CS. Psychosocial interventions may appear more effective than they truly are due to the overestimation of effect sizes resulting from inadequate placebo controls (a fact that has been demonstrated in this meta-analysis where larger effect sizes were found when CS was compared with non-active controls than when compared with active controls). Studies examining the true efficacy of

psychosocial interventions should aim to at least to be single-blinded (i.e. blinding of participants), with active placebo controls. It is, of course, difficult to blind participants in psychosocial interventions, and such blinding raises ethical issues, but it is not impossible, as demonstrated in a recent CBT trial¹⁴². Ultimately, it is clear from our meta-analyses that more randomised, single-blinded, active placebo controlled studies are required to properly assess the efficacy of cognitive interventions in dementia.

2.7.2 SPECIFIC COGNITIVE OUTCOMES IN CT AND MCTS STUDIES

Examination and meta-analyses of specific cognitive functions revealed that the most commonly assessed domains were episodic memory and executive function. Studies that taught mnemonic strategies usually taught visualisation of words to be learnt, or association between objects and names. This is consistent with the primary training strategies of many of the studies, which sought to specifically target episodic memory or teach executive strategies. Cognitive training RCTs demonstrated significant training related improvements in executive function and episodic memory (although only when all studies were included in the meta-analysis). Notably no MCTS study demonstrated any significant improvements in the specific outcomes assessed.

An interpretation of these results is that training effects are more likely when the outcomes reflect the focus of the training intervention. Many MCTS trials contained a wide range of activities, compared to the focused approach of CT. Perhaps unsurprisingly, the most efficacious studies were those that concentrated on the most specific training approaches^{93 125 126}.

The criticism of this approach is reflected in the general cognitive outcome data, that there is little evidence of transfer to general outcomes, however in this analysis, only 4 CT studies included general cognitive outcomes.

Of relevance to the current study, there was no evidence of overall improvement in general WM tasks. However of the two studies assessing verbal WM, rather than spatial WM, one reported a moderate-large significant effect of training ($g = 0.65$ (95% CI: 0.02, 1.29)⁹³, and the other a moderate-large but insignificant effect ($g = 0.74$ (95% CI: -0.16, 1.659)¹²⁴. And in neither of these studies was the intervention primarily targeting WM. The one study that targeted executive WM using a dual task training paradigm demonstrated significant improvements in divided attention ($g = 0.816$ (95% CI: 0.288, 1.344).

Overall these results remain consistent with other recent reviews that call for further studies, where specific cognitive domains are targeted using theoretically driven training paradigms in AD^{49 75}. A focus on WM appears to be one of the most promising avenues for cognitive training in healthy adults⁵², and chunking is a strategy that may underlie efficacy⁵³. The evidence from the current meta-analysis that targeted training may improve episodic memory and executive function provides further impetus for the current study, which used chunking, an executive WM strategy, and assessed outcomes in WM, episodic memory and executive function. This randomised, placebo- controlled trial of chunking training in AD is therefore novel, timely and justified from the literature.

Section/topic	Checklist item	Page number/ Figure/Table
<i>Title</i>		
Title	Identify the report as a systematic review, meta-analysis, or both.	1
<i>Abstract</i>		
Structured summary	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<i>Introduction</i>		
Rationale	Describe the rationale for the review in the context of what is already known.	4
Objectives	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
<i>Methods</i>		
Protocol and registration	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	n/a
Eligibility criteria	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Figure 2-1
Study selection	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	State the principal summary measures (e.g., risk ratio, difference in means).	6,7
Synthesis of results	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7
Risk of bias across studies	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
<i>Results</i>		

Study selection	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7,8, Figure 2-2
Study characteristics	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 2-7
Risk of bias within studies	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Table 2-8
Results of individual studies	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8,9 Figs 2,3,4
Synthesis of results	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8,9, Table 2-2
Risk of bias across studies	Present results of any assessment of risk of bias across studies (see Item 15).	8,9
Additional analysis	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10, Table 2-3,
<i>Discussion</i>		
Summary of evidence	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11,12
Limitations	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12,13

Table 2-6: PRISMA checklist

Study	Setting	Severity of dementia MMSE (SD)	Frequency and format	Tx group (length of Tx period (weeks))	Comp group	Axs in weeks	N after randomization		Mean age	% female	GEN COG outcomes and calculated mean difference. ^a	Description of Intervention
							IG	CG				
Avila et al (2007) ¹¹⁵	2 GPs as OP, 1 GP at home	1) 20 (4), 2) 20.8 (5), 3) 18.4 (5.1)	GP 60 min 1 x wk, IND 40 min 1 x wk	22	1) GP vs IND 2) GP vs home 3) IND vs home	0 , 22	GP 5 IND 6 Home 5		73.8	82.4	GP vs. IND: ADAS-Cog= -2.16 MMSE= -0.84 GP vs. HOME: ADAS-Cog= -8 MMSE= 3.2 IND vs. HOME: ADAS-Cog=-5.84 MMSE=4.04	CS and CR
Baldelli et al (1993) ⁹⁵	IP	IG: 20.1 (4.7) CG:21.3 (5.1)	GP 1 hour 3 x wk	12	NA	0, 12 (post) 24 (f/u)	13	10	84.5	100	MMSE= 7.4 f/u MMSE= 6.5	CS
Baldelli et al (2002) ⁹⁶	IP	20.77	GP hr/day 5 x wk	4	NA	0, 16	71	16	80	70.1	MMSE= 2.46	CS
Beck et al (1988) ¹²⁴	IP and care home	15 -20	IND, 30-40 min 3 x wk	6	NA	0, 6	10	10	IG 74, CG 76	IG 50% CG 70%	n/a	CT
Bottino et al (2005) ⁹⁷	OP	IG:21.29 (3.8) CG-23.5 (3.27)	90 min 1 x wk	20	NA	0 and 20 (post)	6	7	73.7	69.2	MMSE= 2.26 ADAS-Cog= -2.6	CS
Breuil et al (1994) ⁹⁸	OP	>9	1 hr 2 x week	5	NA	0 and 6 (post)	32	29	77.2	60.5	MMS= 2.1	CS:
Buettner et al (2011) ⁹⁹	Care homes	IG:25.2 (3.3) CG:25.4 (2.8)	1 hr 2 x wk	4	Active	0 and 4	48	48	81.6	80.5	MMSE= 1.55	CS

Burgener et al (2008) ¹⁰⁰	community	IG:24.8 (3.5) CG: 22.9 (5.2)	1)taichi-1 hr, 3 x wk. 2)Cog: 90 min, 2 x wk: 3)support group: 90 min, 2 x wk	40	Active	0, 20, 40 (post)	24	19	76.95	47	MMSE= 0.9	CS
Buschert et al (2011) ¹¹⁶	OP	IG:24.5 (1.6) CG: 25.3 (1.5)	GP 20 x 2 hr	24	Active	0, 24 (post)	8	7	75.9	53	ADAS-Cog= -0.7 MMSE= 1.4	MCTS
Cahn-Weiner et al (2003) ¹²⁸	OP	IG:24.3 (2.2), CG 25.1 (1.7)	GP, 6 1 x wk	6	Active	6, 14	17	17	IG: 77.8 CG; 76	59%	n/a	CT
Chapman et al (2004) ¹⁰¹	community	20.87 (3.55)	GP 1.5 hr , 1 x wk	8	NA	0, 16 (post), 32 f/u 48 f/u	28	26	76.38	54	MMSE= 0.02 ADAS-Cog= 0.78 32 f/u MMSE= 0.9 32 f/u ADAS-Cog= -0.52 48 f/u MMSE= 1.92 48 f/u ADAS-Cog= -3.42	CS
Coen et al (2011) ¹⁰²	Care home	Mild-mod (10-23)	14 x 45 min 2 x wk	7	NA	0 and 7 (post)	14	13	79.85	52	MMSE= 2.9 ADAS-Cog= 2.1	CS
Davis et al (2001) ¹¹⁷	OP	IG: 21.84(4.03) CG: 22.78 (4.45)	1 hr 1 x week	5	Active	0 and 5 (post)	19	18	70.6	57	MMSE= -0.06	MCTS
Ferrario et al (1991) ¹¹³	IP	Range 18-25	GP 1 hr 5 x wk	24	NA	0, 12, 24	13	6	82.5	42	Clifton Assessment Schedule (CAS)= 1.3	CS

Galante et al (2007) ⁹¹	OP (unclear)	IG: 22.9 CG:23.1	IND 60 min , 3 x wk	4	Active	0, 4 (post), 12, 36 (f/u)	7	5	76	No info	MODA= -3.5 MMSE= -1.7 12 f/u MMSE=- 2.6 12 f/u MODA= -4.1 36 f/u MMSE= 3.2	CT
Graessel et al (2011) ¹⁰³	Care home	IG: 15.4 (5.4) CG:13.8 (5.4)	GP 2 hrs 6 x wk	12 months	NA (TAU)	0, 52	50	48	85.1	80	ADAS-Cog= -3.8	CS
Haight et al (2006) ¹⁰⁴	Care home	Mean 17.8	'Intervention takes 8 hours'	8	NA (TAU)	0, 8 (post)	15	16	unclear-range 60-99	81	MMSE= 7.27	CS
Heiss et al (1994) ⁹²	OP	IG: 20.55 CG: 20.23	IND 1 hr 2 x wk	6 months	ACTIVE (social support)	0, 8,16 and 24 (post)	18	17	66.3	45.5	MMSE= -0.28	CT
Jelcic et al (2012) ⁹³	OP	IG 24.4 (2.8) CG: 25 (2.6)	1 hr, 2 x wk	3 months	ACTIVE	0,12 (post), 36(f/u- for IG only)	20	20	82.4	82.5	MMSE= 3	CT
Kawashima et al (2005) ⁹⁴	Care home facilities	IG 19.9 CG 19.6	IND 20 min 2-6 x wk	6 months	NA (TAU)	0, 24	16	16	85.7		MMSE 1.9	CT
Koltai et al (2001) ¹¹⁸	OP	IG: 22.9 (3.6) CG: 26.6 (2.5)	GP 5 x 1 hr IND 'mean =6'	Unclear- approx 6	NA (wait list)	0 and post (average 6.3)	IND 8 GP 8	8	73.4	No info	MMSE= -0.96	MCTS
Kurz et al (2011) ¹¹⁹	OP	IG: 25.01 CG: 25.11	1 hr/ week	12	NA (TAU)	0,12,(post) 36 (f/u)	100	101	73.7	44	36 f/u MMSE= 0.74	CS and CR

Lai et al (2004) ¹¹⁴	Care home	IG: 8.3 (5.1), CG 9.3 (5.1), (active) CG:10.7 (6.1) (NA)	30 min 1 x wk	6	Active and NA	0, 6 (post) 6 (f/u)	36	35, 30 (NA)	85.7	68.3	MMSE= 1.47 (ACTIVE) 0.78 (NA) 6 f/u MMSE (ACT)= 4.39 6 f/u MMSE (NA)= 2.82	CS
Luttenberger et al (2012) ¹⁰⁵	Care home	IG: 15.57 (4.83) CG:14.14 (5.45)	GP 2 hrs, 6 x wk	12 months	NA (TAU)	0, 88 (f/u)	50	48	84.37	81.4	(f/u) ADAS-Cog=-3.86	CS
Maci et al (2012) ¹²⁰	OP	IG: 17.5 (2.7) CG:18.2 (2.9)	4 hrs, 5 x wk	12	NA (TAU)	0, 12 (post)	7	7	72.65	57	MMSE= 1	MCTS
Neely et al (2009) ¹²⁵	At home	18.6 -22.9	IND1 hr 1 x wk	8	NA	0, 8	10 10	10	mean 74.6- 77	50%	n/a	CT
Niu et al (2010) ¹²¹	IP	IG: 16.93 (3.02) CG:17.31 (3.24)	IND 45 min 2 x wk	10	Active (communication exercise)	0 and 10	16	16	79.8	21.9	MMSE= 1	MCTS
Onder et al (2005) ¹⁰⁶	community	IG:20.2 (3.3) CG: 19.9 (3)	IND 30 min 3 x wk	25	NA (TAU)	0 , 25 (post)	79	77	75.8	72	MMSE= 1.3 ADAS-Cog= -2.9	CS
Onor et al (2007) ¹⁰⁷	Unclear-OP/community	IG: 23.1 (4.3) CG: 20 (2.2)	pts: 60 min 3 x wk. Carer: 60 min 1 x wk format unclear	16	NA (TAU)	0, 8, 16 (post)	8	8	70	43.8	MMSE= 0 Total MODA= 1.8	CS
Quayhagen et al (1995) ¹²²	community	>90 on Mattis (mild-mod)	60 min, 6 x wk	12	1)ACT 2)NA (wait)	0, 12 (post) 36 (f/u)	25	28 25	73.6	35	Mattis DRS= 5 (active), 7.7 (NA) 36 f/u Mattis=3.8 (active), 10.4 (NA)	MCTS

Requena et al (2006) ¹⁰⁸	Community (day centre)	CS- 19.44 CS + drug- 22.95 Drug- 21.17 Wait-19.39	45 min, 5 x wk, with exercises done at home on weekends	104	1)NA (drug only) 2)Waiting 3)CS + drug	0, 52, 104 (post)	CS- 18 CS + drug- 20	Drug- 30 Wait- 18	76.97	71.8	MMSE= 5.99 ADAS-Cog= -11.94	CS
Schwenk et al (2010) ¹²⁶	OP	17 - 26	GP 2 hr 2 x wk	12	Active	0, 12	26	35	81.9	IG 65%, CG 62.9%	n/a	CT
Spector et al (2001) ¹⁰⁹	Day centre residential home	IG:11.5 (4.4), CG: 15.5 (4.4)	GP 45 min 2 x wk	7.5	NA (TAU)	0, approx 7.5 (post)	21	14	85.7	No info	MMSE= 3.1 ADAS-Cog= -5.3	CS
Spector et al (2003) ¹¹⁰	Day centre residential homes	IG:14.2 (3.9) CG: 14.8 (3.8)	GP 45 min 2 x wk	7	NA (TAU)	0, 7 (post)	115	86	85.3	78.6	MMSE= 1.3 ADAS-Cog= -2.2	CS
Tadaka et al (2007) ¹¹¹	Day centre	AD IG:14.6 (5.3) CG: 14.9 (4.6) VD IG:19.8 (5) CG- 18.2 (5.4)	60-90 min, 1 x wk	8	NA (TAU)	0, 8 (post), 24 (f/u)	30 (12 AD, 18 VD)	30 (12 AD, 18 VD)	83.1	70	MMSE= 0.1 (AD) 3.6 (VD) 24 f/u MMSE = 2.7 (VD), -0.1 (AD)	CS
Tarraga et al (2006) ¹²³	Day centre	CT/CS/drug 20.6 CS/drug: 22.5 Drug: 22.83	IND CT 20 min 3 x wk (computer based) GP CS 3.5 hrs 5 x wk	24 s	NA (MEDS) MCTS vs. CT	0, 12, 24	MCTS/ MEDS 18 CS/ME DS 16	MED S 12:	76.7	84.8	CS+DRUG vs. DRUG: MMSE= 1.63 ADAS-Cog= -0.71 MCTS+DRUG vs. DRUG MMSE=1.47 ADAS-Cog= -1.07 MCTS vs. CS MMSE= 1.34 ADAS-Cog= -2.19	CS MCTS
Wang et al (2007) ¹¹²	Care homes	IG: 14.33 CG: 14.33	60 min 1 x wk	8	NA (TAU)	0 and 8 (post)	51	51	79.34	51	MMSE= 1.88	CS

Zarit et al (1982) ¹²⁷	Community	Unclear	GP 1.5hr 2 x wk	3.5	1		14	10	74.08	No info	N/A	CT
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Table 2-7: Characteristics of studies included in the meta-analyses.

IP= inpatient, OP= outpatient, IG= Intervention Group, CG= Control Group, GP= Group sessions, IND = Individual sessions, NA= non-active control, TAU= Treatment as usual, post= post-intervention, f/u= follow-up, MMSE- Mini mental state examination, ADAS-Cog- Alzheimer's Disease Assessment Scale_ cognitive subscale, CS= cognitive stimulation, CT= cognitive training, MCTS= mixed cognitive stimulation and training, AD= Alzheimer's Disease, VD= vascular dementia, MODA= Milan Overall Dementia Assessment, MATTIS DRS= Mattis dementia rating scale

^aMMSE/CAS/MODA/MATTIS- positive score favours intervention. ADAS-Cog- negative score favours intervention.

Study	Randomization Sequence generation (A)	Randomization Allocation concealment (B)	Blinding of outcome assessors (C) [†]	Incomplete outcome data (D)	Selective reporting of outcome data (E)	Number. of IN/ UN ratings	Reasons for quality ratings
Avila et al (2007)	AQ	AQ	AQ	AQ	AQ	0	
Baldelli et al (2002)	IN/UN	IN/UN	IN/UN	AQ	AQ	3	No information about A, B. States that subjects were divided into groups, however correspondence by email to Cochrane group confirmed that studies were randomised. No information about C
Baldelli et al (1993)	IN/ UN	IN/UN	IN/ UN	AQ	AQ	3	No information about A, B. States that subjects were divided into groups, however correspondence by email to Cochrane group confirmed that studies were randomised. No information about C
Bottino et al (2005)	AQ	AQ	AQ	AQ	AQ	0	
Breuil et al (1994)	IN/UN	IN/UN	PAQ	PAQ	IN/ UN	3	No information about A or B; E- some tasks were discarded and others grouped.
Buettner et al (2011)	IN/UN	IN/UN	AQ	IN/UN	AQ	3	No information about A, B. D- sig difference in dropouts between groups and not included in analysis.
Burgener et al (2008)	IN/UN	IN/UN	IN/UN	IN/UN	AQ	4	No information about A, B or C. Patients could self refer. No mention of method of randomisation D: reason for 3 of 5 drop out in control group- 'increased disability', whilst reason for 3 of 5 in exp group- 'not needing the intervention
Buschert et al (2011)	AQ	AQ	AQ	AQ	AQ	0	
Cahn-Weiner et al (2003)	AQ	AQ	PAQ	PAQ	AQ		
Chapman et al (2004)	AQ	AQ	AQ	PAQ	AQ	0	D: uneven number of dropouts in each group (8 in exp group, 5 in donepezil only group)
Coen et al (2011)	IN/UN	IN/ UN	AQ	AQ	AQ	2	No information about A or B
Davis et al (2001)	IN/UN	IN/UN	PAQ	PAQ	AQ	2	No information about A or B; 4 patients did not crossover from the placebo group due to lack of interest in continuing the study

Ferrario et al (1991)	IN/UN	IN/UN	IN/UN	AQ	AQ	3	No information for A,B or C
Galante et al (2007)	PAQ	PAQ	AQ	IN/ UN	AQ	1	A and B states 'randomly assigned to one of two groups in order of recruiting' D: 1 drop out in control group, leaving groups mismatched (7 vs 4), dropouts not included in analysis
Graessel et al (2011)	AQ	AQ	AQ	AQ	AQ	0	
Haight et al (2006)	IN/UN	IN/UN	IN/UN	IN/UN	AQ	4	No information about A, B – states 'were assigned randomly by the researchers' no information about C or D
Heiss et al (1993)	IN/UN	IN/UN	IN/UN	IN/UN	AQ	4	No information about A,B, C or D
Jelcic et al (2012)	AQ	IN/UN	AQ	AQ	AQ	1	Unclear info about B
Kawashima et al (2005)	IN/UN	IN/UN	IN/UN	AQ	AQ	3	No information about A, B or C
Koltai et al (2001)	IN/UN	IN/UN	IN/UN	PAQ	PAQ	3	No info about A, B or C. D: some missing data but probably unrelated to study. E: reports results stated in methods, however adds subsequent subjective 'anosognosia rating' and re analyses some results using this
Kurz et al (2012)	AQ	AQ	AQ	AQ	AQ	0	
Lai et al (2004)	IN/UN	IN/UN	AQ	PAQ	AQ	2	No information about A and B- just states that 'were randomly assigned to groups'
Luttenberger et al (2012)	AQ	AQ	AQ	PAQ	AQ		
Maci et al (2012)	AQ	PAQ	AQ	AQ	AQ		
Neely et al (2009)	IN/UN	IN/UN	IN/UN	AQ	AQ	3	No information given about A, B or C states that 'first 30 couples who agreed to participate were randomly assigned'
Niu et al (2010)	AQ	AQ	AQ	AQ	AQ		
Onder et al (2005)	AQ	AQ	AQ	AQ	AQ		
Onor et al (2007)	IN/UN	IN/UN	IN/UN	AQ	AQ	3	No information about A,B just states that 'simple randomisation was used' No information about C
Quayhagen et al (1995)	IN/UN	IN/UN	PAQ	IN/UN	PAQ	3	Unclear information about A,B or D

Requena et al (2004 and 2006)	IN/UN	IN/UN	IN/UN	IN/UN	AQ	4	A and B 'subjects were randomly distributed in groups at the time they arrived at the centre': No information/Unclear C and D
Schwenk et al (2010) ¹²⁶	AQ	AQ	AQ	PAQ	AQ		
Spector et al (2003)	AQ	AQ	AQ	IN/UN	AQ	1	No information about D
Spector et al (2001)	AQ	AQ	IN/UN	PAQ	AQ	1	C: outcome measures not blinded
Tadaka et al (2007)	AQ	PAQ	AQ	IN/UN	AQ	1	Unclear information for D
Tarraga et al (2006)	IN/UN	IN/UN	IN/UN	PAQ	PAQ	3	Unclear/no information about A,B and C
Wang et al (2007)	PAQ	IN/UN	PAQ	PAQ	AQ	1	B- Unclear information
Zarit et al (1982)	IN/UN	IN/UN	IN/UN	AQ	AQ	3	No information about A, B or C

Table 2-8: Quality ratings for studies included in the meta-analyses
AQ= adequate, PAQ= partially adequate, IN/UN= inadequate/ unclear

Chapter 3 METHODS – RCT

3.1 SUMMARY OF TRIAL

The study followed a parallel single-blinded, randomised controlled trial design. Participants were randomly allocated to a cognitive training or active control condition. Both groups were assessed with a battery of neuropsychological assessments and performed a digit span task whilst undergoing fMRI. The neuropsychological assessments and fMRI were performed pre- and post- interventions, which consisted of 18 sessions delivered over approximately 6 weeks.

3.2 RECRUITMENT

Participants were recruited from Mental Health for Older Adults (MHOA) services of the South London and Maudsley NHS Mental Health Foundation Trust (SLAM). Memory clinics and community mental health teams (CMHTs) were contacted and provided with an information sheet describing the study. Potential participants were also identified from monthly SLAM dementia neuroimaging meetings and from the Institute of Psychiatry (IOP) Dementia Case Register. The Case Register is a database of individuals with dementia collated by specialist dementia research nurses in the Department of Old Age Psychiatry at the IOP. Individuals in this database have previously consented to being involved in research and most have been receiving annual contact with researchers for assessment of cognitive function as part of a longitudinal study. Some participants had been involved in other research studies over the preceding 2 years; however no participant approached to take part in the study was currently involved in any other interventional study. Potential participants were initially approached by members of their clinical care teams or by the specialist nurses to ascertain whether they would be interested in taking part in the study. If verbal consent was given, their contact details were passed to the researcher. No patients self-referred to the study.

(See Appendix 1 for examples of all patient information sheets and consent forms).

3.3 INCLUSION CRITERIA

Inclusion criteria were:

- 1) Diagnosis of possible or probable Alzheimer's disease. The diagnosis was made by a multidisciplinary team assessment/clinical services, based on ICD criteria and NINCDS-ADRDA criteria for diagnosis of AD⁷. A diagnosis of mixed dementia was permitted. If a participant was, in the opinion of the clinical team, at the point of transition from a diagnosis of MCI to AD due to evidence of cognitive and functional decline, they were also considered for inclusion.
- 2) Age 65 or above

3.4 EXCLUSION CRITERIA

Exclusion criteria were:

- 1) Diagnosis of significant co-morbid neurological or psychiatric illness
- 2) Significant visual or auditory impairment that would make it difficult for the participant to perform the tasks.
- 3) Primary diagnosis of fronto-temporal dementia, Lewy body dementia, vascular dementia or other non AD dementia.
- 4) Past medical or surgical history that would contra-indicate undergoing an MRI scan at 3T. As any previous surgery could potentially have resulted in the retention of iron-containing clips, all participants who had a history of surgery required evidence that there were no metallic implants still present. This was either from surgical notes or plain x-ray imaging that could clearly demonstrate the absence of metal. As many participants had had surgical procedures several decades ago, it was not always possible for contemporaneous surgical notes to be accessed, and if this was the case participants were excluded from the study. Any cases where there was a query over safety were discussed with radiographers in the MRI department in advance of the scan booking.

3.5 INFORMED CONSENT PROCEDURE

Potential participants who were identified by research nurses or members of clinical teams were asked for verbal consent to be contacted by the study researcher (JH). The researcher then contacted the participant by telephone, to briefly describe the study and ask if they would like to receive further information. If they agreed, an information sheet was then sent to the participant and a follow up phone call was made after 2-3 weeks. If the participant remained interested in taking part in the study, an initial home visit was arranged. At this initial visit the study was described, and potential participants and their carers were encouraged to ask any questions. If they remained interested in taking part in the study, they were asked to consent to provide details about their medical history and for the researcher to contact their GP or access relevant hospital medical records to ensure their safety to undergo MRI. A follow-up visit was arranged after approximately a further 2-3 weeks, and if a review of medical records had confirmed that the participant was safe to undergo MRI, a date was given for the initial MRI scan. The reasons for the study, including the design and randomisation, were discussed, and participants were again given the opportunity to ask any questions about the study. All participants were assessed for capacity to make a decision regarding their participation in the trial. If any participant lacked capacity to make an informed decision regarding participation they were excluded. Participants were then asked to complete the consent form. A mobile telephone number was left with the information sheet and participants and carers were encouraged to contact the researcher at any time with questions or concerns they may have had about the study.

3.6 RANDOMISATION

An internet based block randomisation program¹⁴³ was used to randomise participants in blocks of 10, with 5 participants randomised to each of the cognitive training and control groups. Participants were randomised following the baseline fMRI scan. The randomization was performed online by an individual not involved in the study, who had no information about, or contact with, the participants. The researcher was then informed of group allocation on a participant by participant basis. This meant the researcher was unable to refer participants for randomisation in a way that could manipulate the group allocation, thus blinding the researcher to the sequence generation and allocation process.

3.7 BLINDING

3.7.1 OF PARTICIPANTS

During discussion of the study, both arms of the study (cognitive training and active control) were presented to participants and their carers as providing a significant amount of cognitive stimulation and potentially leading to benefits. However, it was stressed that there were no guarantees that participants would experience any personal benefit or improvement in cognition as a result of training. It was clearly stated in the information sheet that participants were randomly allocated to the two different groups, however once training was commenced none of the participants asked to which of the groups they had been allocated, and all participants considered they were engaging in cognitive training. In this way participants were effectively blinded as to their allocation for the duration of the study.

3.7.2 OF RESEARCHER

Due to a single researcher being responsible for all aspects of the study (recruitment, assessment, intervention and analysis), it was not possible to blind the researcher to allocation post randomisation.

3.8 BASELINE ASSESSMENTS

The following assessments were performed at baseline to ensure participants met inclusion criteria and to provide demographic and baseline information for the study.

- 1) Age
- 2) Gender
- 3) Years of education
- 4) National Adult Reading Test (NART)¹⁴⁴, as a test of pre-morbid IQ.

The NART requires participants to read aloud a list of 50 irregular words. The word list is presented to the participant, who is asked to read each word out loud. A point is scored for the correct pronunciation of each word. The total score can be used to estimate a pre-morbid

IQ score. The NART is widely used to estimate pre-morbid intellectual ability, including in dementia patients¹⁴⁵. Pre-morbid IQ was estimated using the equation:

$$IQ = 127.8 - 0.78 \times (NARTerrors)^{146}.$$

- 5) Geriatric Depression Scale (GDS)¹⁴⁷, to exclude significant depressive illness. The 30 point GDS was used to assess current depressive symptoms. It has been extensively validated in older adults¹⁴⁸. Each question is scored with either one point for 'yes' or zero for 'no'. A score of 11-20 indicates mild depression and a score of 21-30 indicates severe depression.
- 6) Hachinski Ischaemic Score¹⁴⁹; Thirteen questions regarding significant cerebro-vascular risk factors or factors considered important in vascular aetiology are asked with a maximum score of 18. A score of 4 or less suggests no evidence for vascular aetiology, whilst a score above 7 is suggestive of vascular dementia.
- 7) Neuropsychiatric Inventory (NPI)¹⁵⁰, to exclude behavioural and psychological symptoms that may affect performance in the study. Twelve areas are assessed in the NPI (delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, sleep and appetite/eating disorders). Each of these areas is scored on a 4 point scale of frequency and a 3 point scale of severity. A caregiver distress score is also produced from a 6 point scale of (0= none, 6= extreme). NPI score is calculated by multiplying frequency x severity score.
- 8) Sensory screening - for handedness and to exclude significant visual or auditory impairment that could influence performance or participation in the study.
- 9) Webster rating scale¹⁵¹- to exclude evidence of significant extrapyramidal or parkinsonian symptoms and signs.

3.9 PRIMARY OUTCOME MEASURES - WORKING MEMORY

The following measures were performed at both baseline and post intervention.

3.9.1 DIGIT SPAN (Figure 3-1)^{15 26}

This is a well established task of verbal working memory²³. Twenty trials of a ladder digit span task were performed^{26 68}. Participants were initially shown a 3 digit sequence and asked to remember the

sequence for a few seconds and then to verbally recall the sequence in order. If they correctly recalled the sequence, then the number of digits to be recalled (span) would increase by 1 for the subsequent trial. Conversely, if the sequence was incorrectly recalled, the next trial would have one less digit. In this way participants would tend to reach and then oscillate around their maximum span. Two versions of this task were performed. A 'structured' version, whereby digits were presented in runs of consecutive numbers or increasing or decreasing in 2s (e.g. 2,4,6,8 or 9,7,5,1,2,3). These structured sequences encouraged chunking. A second 'random' version of this task was also performed. Here a random number generator was used to ensure the digits were presented in as random a sequence as possible. Previous studies have demonstrated that structured sequences encourage chunking and improve span span in healthy young controls, healthy elderly controls and AD patients^{26 68}.

The task was performed on a laptop computer. Digits were presented for 1000ms with a 500ms delay between digits. After the final digit was presented there was a further delay of 500ms, before the word 'RESPOND' appeared on the screen. At this prompt the participant verbally recalled the digits in order, and the researcher typed them into the computer. If the digits had been correctly recalled the word 'CORRECT' was presented on the screen, if incorrect the words 'TRY AGAIN' were presented. There was then a delay of 500ms before the next trial commenced. All trials started with the words 'NEXT TRIAL' together with a number to inform the participant how many digits would be presented in the subsequent span.

The timings of the presentation of the digits and length of trials were based on pilot data⁶⁸, which ensured that participants with AD were given enough time to attend and respond to the stimuli. The length of the starting span (3 digits) was also chosen following the results of a pilot study demonstrating that the majority of participants with AD could perform this successfully⁶⁸. (Figure 3-1).

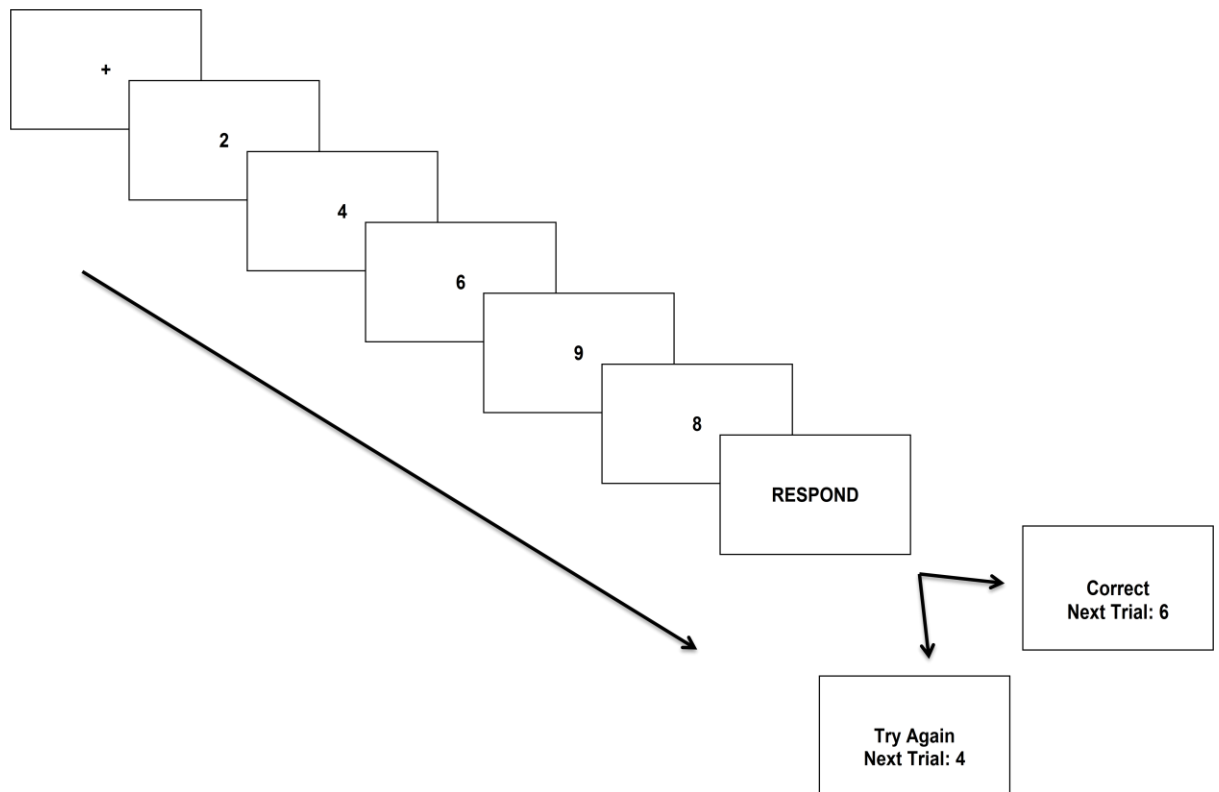


Figure 3-1: Schematic of digit span task, showing structured trial.

3.9.2 SPATIAL SPAN

This is a task of spatial working memory, based on Corsi's block tapping task¹⁵², which has been used extensively in participants with AD^{17 153}. In this task, a 4 x 4 grid of red squares was presented on a computer screen. Initially 3 blocks sequentially flashed blue for 1000ms before returning to red. Participants had to remember which blocks had changed and the sequence. After a 500ms delay, an audible tone sounded and using a touch-screen, participants had to directly press on the blocks that had changed colour, in the correct sequence. If the participant correctly recalled the sequence, the following sequence increased by one, incorrect recall resulted in one less block being highlighted in the next sequence. In this way participants would reach their maximum span and oscillate around this. Again, two versions of this task were performed. A 'structured' version, whereby blocks tended to be presented in the same row or column, or in recognisable shapes. Secondly, a 'random' version was performed, where blocks were presented in random combinations. The structured version has been shown to encourage the use of chunking both in young participants²⁴, elderly controls and

participants with early AD⁶⁸. Figure 3-2 shows an example of the spatial span task and Figure 3-3 shows examples of structured and random trials for both digit and spatial span tasks.

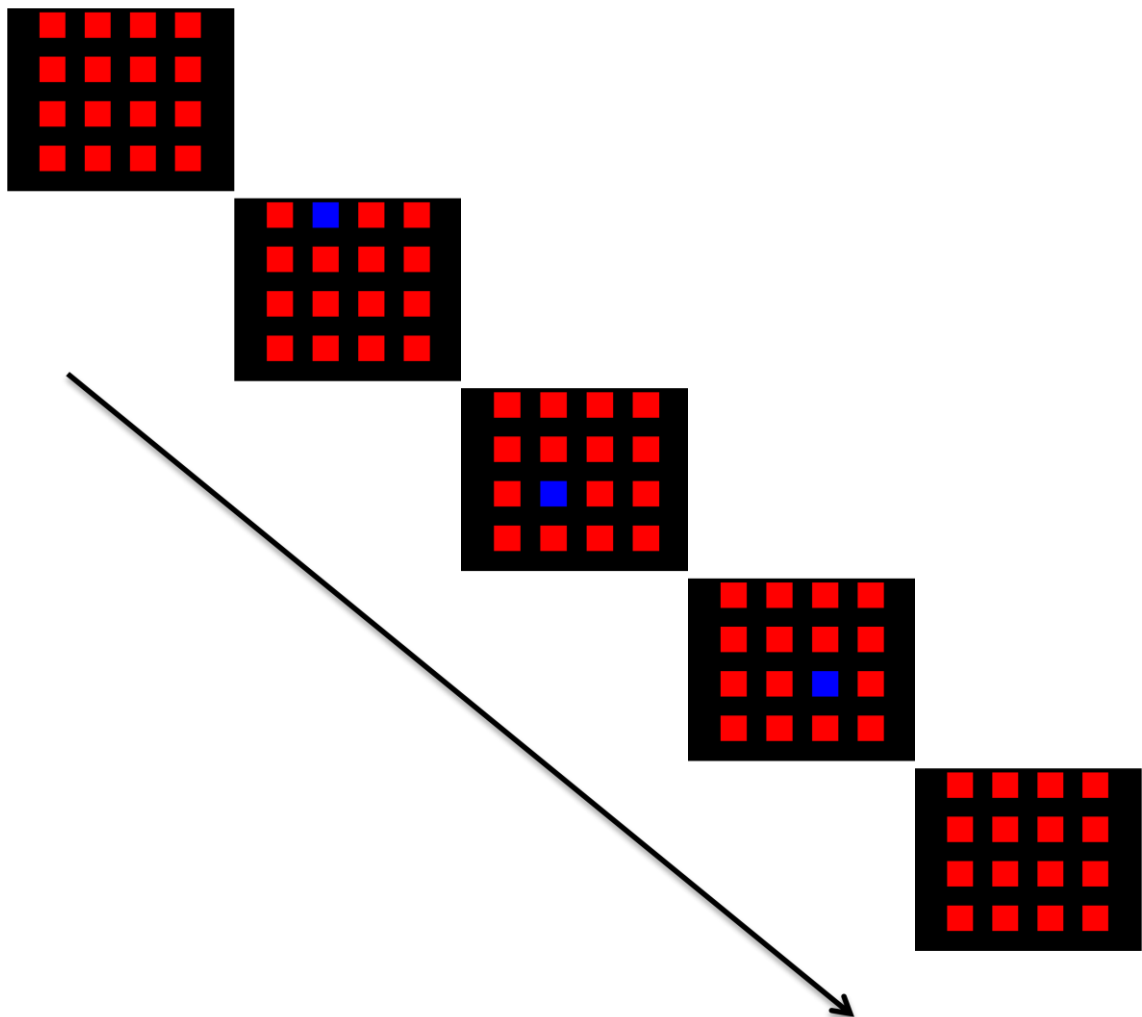


Figure 3-2: Schematic of spatial span task, showing a trial of 3 structured locations

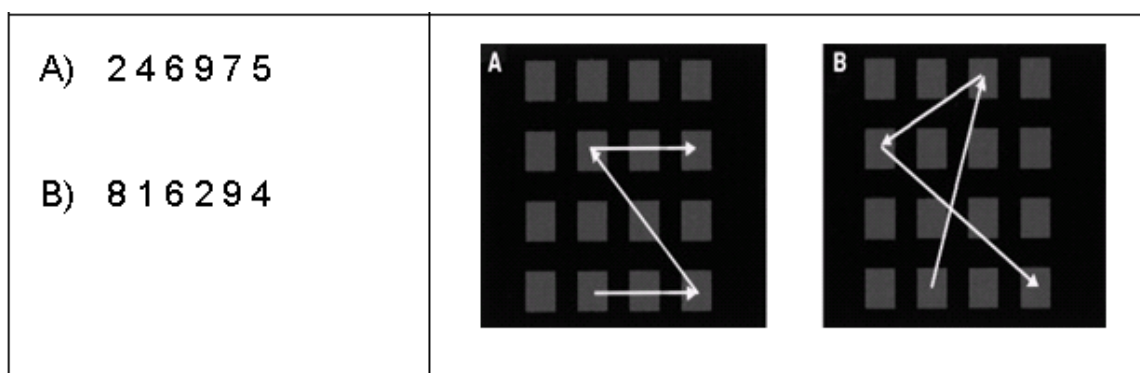


Figure 3-3: Examples of A) STRUCTURED and B) RANDOM trials for both digit and spatial span tasks

3.10 SECONDARY OUTCOME MEASURES

The following measures were performed at both baseline and post intervention.

3.10.1 GENERAL COGNITIVE FUNCTION

3.10.1.1 MINI MENTAL STATE EXAMINATION (MMSE)⁷¹

This is a widely used 30-point pen-and-paper assessment incorporating assessments of orientation (10 points), immediate and delayed recall (6 points), reading, repetition, writing and copying of a shape (4 points), object recognition (2 points), following a three-stage instruction (3 points) and attention (5 points). Points are scored for each correct response, with a maximum score of 30.

3.10.1.2 ALZHEIMER'S DISEASE ASSESSMENT SCALE - COGNITIVE SECTION (ADAS-Cog)⁷²

This is a widely used 70 point pen-and-paper assessment involving eleven subsections that evaluate word recall, word finding and naming, following commands, orientation, copying shapes, performing a 5 stage task, recall of test instructions, word recognition, spoken language ability and language comprehension. It is reverse scored, therefore higher scores represent greater cognitive impairment.

3.10.2 EPISODIC MEMORY

3.10.2.1 LOGICAL MEMORY I AND II

This is a task of verbal episodic memory taken from the Wechsler Memory Scale¹³¹. Participants are read a short story and asked to remember it. As soon as the examiner has finished reading it, they are asked to recall as much of the story as possible (LM I). They are then distracted by performing other tasks, and 25 minutes later asked to recall the story again (LM II). Each part is scored for 25 specific and 7 thematic components, with a total score of 32 points.

3.10.2.2 PAIRED ASSOCIATE LEARNING TASK (PAL)¹⁵⁴

This is a task of visuo-spatial episodic memory that is sensitive to episodic memory deficits in early AD^{155 156} (Figure 3-4). A number of boxes are presented at different locations on a computer screen. Each box covers a picture. The boxes are initially shown, followed by the pictures under each box. Each picture is then presented in the middle of the screen and the participant has to recall which picture appeared under which box, therefore testing both object and location recall. If a participant correctly recalls all the pictures, the next set of boxes has one more box/picture combination. If an error is made a new set of boxes are presented, with one fewer box/picture. If 3 errors are made, the task ends. The task was performed by the participant verbally stating which box they wished to select and the experimenter clicking the corresponding box on the screen.

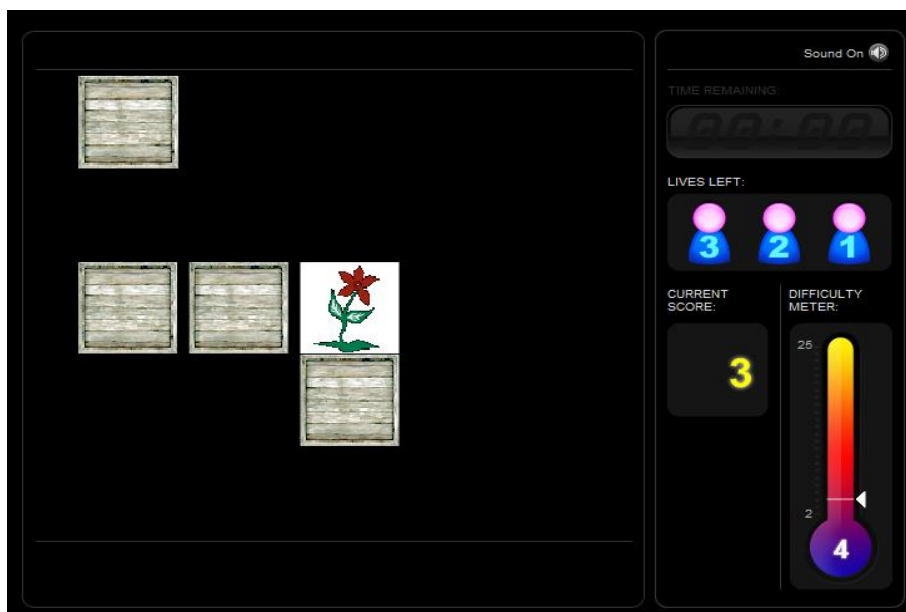


Figure 3-4: Screenshot of the Paired Associates Learning Task. The participant is required to recall in which of the boxes the flower shown in the centre of the screen was hidden.

3.10.3 EXECUTIVE FUNCTION

3.10.3.1 GRAMMATICAL REASONING TASK (GR)¹⁵⁷.

This is a test of executive functioning/verbal reasoning¹⁵⁸ (Figure 3-5). In this task a picture of a square and circle are presented on a computer screen. A sentence describing the relationship between the circle and square is presented above the picture and the participant has to choose whether the sentence describing the picture is true or false. The participant has 90 seconds to answer as many true/false questions as they can. This was done by the participant verbally responding true or 'false' and the experimenter clicking the corresponding button on the screen.

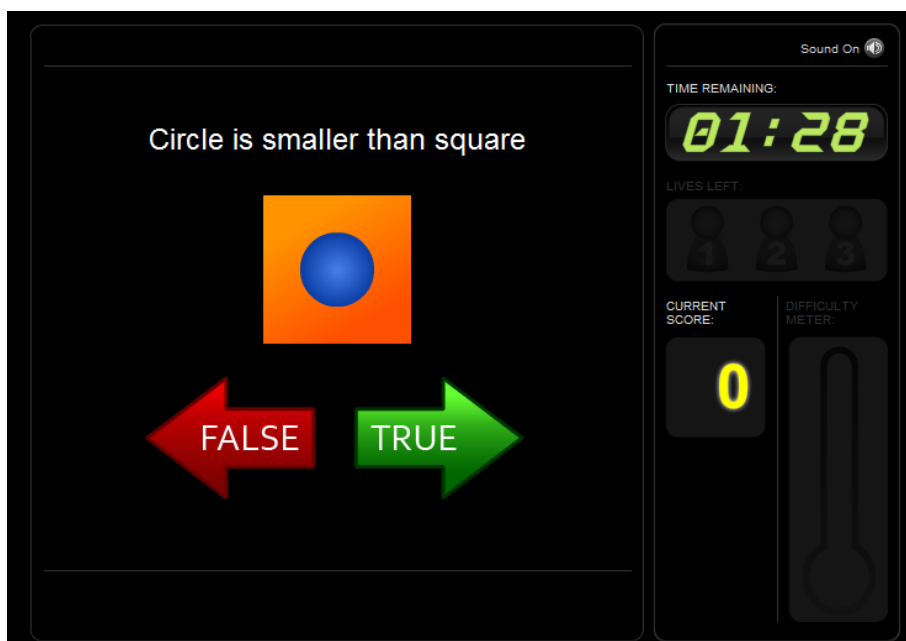


Figure 3-5: Screenshot of the Grammatical Reasoning Task.
The participant has to decide whether the statement describing the circle and square is true or false.

3.10.3.2 ODD ONE OUT TASK (OOO)^{157 159}

This is a test of executive functioning/reasoning (Figure 3-6). In this task a 3 x 3 grid of objects are presented on a computer screen. Each object may be made of up of one or multiple shapes or colours. One object differs from all of the others, owing to it being a different shape, combination of parts or colour. The participant has to choose verbally which object they think is the 'odd one out'. The participant has 3 minutes to answer as many trials as possible in the time.

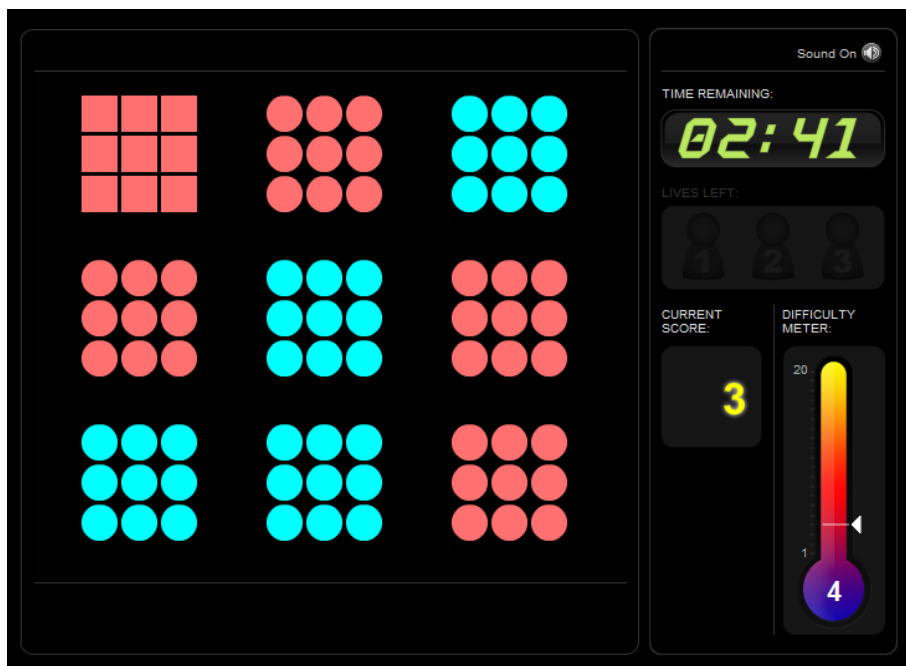


Figure 3-6: Screenshot from the Odd One Out Task.
The participant is required to select which of the 9 objects is the odd one out.

3.10.3.3 SELF ORDERED SEARCH (SOS)

This is a test of executive functioning/planning¹⁵⁹ (Figure 3-7). In this task a series of boxes are presented on a screen. The aim is to search through the boxes in order to find a gold coin hidden in one of the boxes. Gold coins appear sequentially in the boxes, with a new coin appearing in one of the remaining boxes after each coin has been found. There are two rules to the task. Firstly, a coin will never be hidden in the same box twice, therefore if a coin has already been found in a box, and the participant looks in that box again, they will lose a “life”. Secondly, if a participant looks in the same empty box twice whilst looking for a coin, they will lose a “life”. The task proceeds with the participant deciding which boxes to look in, and continues until a gold coin has been found in each box. If an error is made, the participant loses a “life” and a new trial is started with one less box. If the participant successfully finds all the gold coins, a new trial begins with one additional box. The task therefore tests the participant’s ability to plan and execute a strategy and also recall the spatial location of boxes searched and coins previously found.

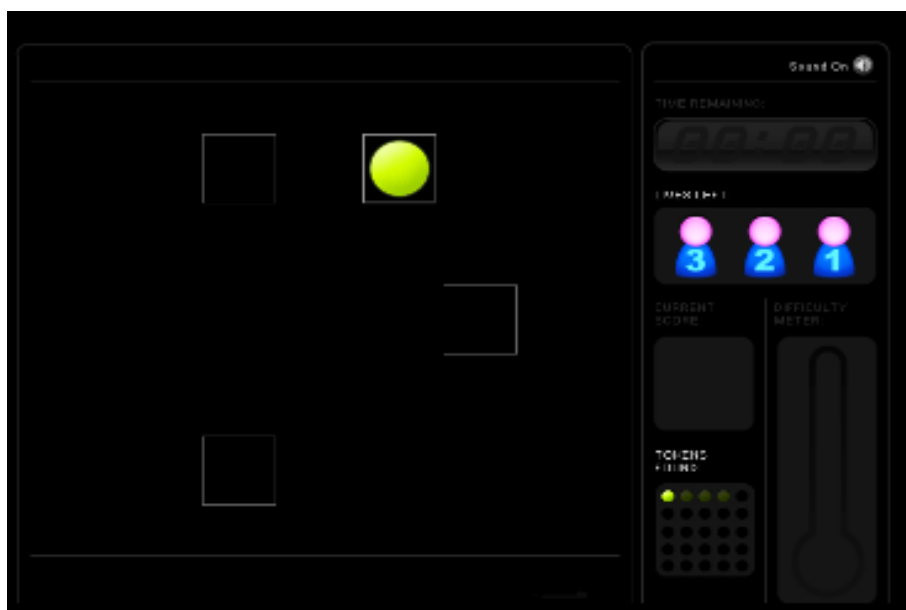


Figure 3-7: Screenshot from the Self Ordered Search task. A gold coin has just been found in the top right box. The participant must now continue to search through the boxes until the three remaining coins are located. However they must not revisit the top right box or the same empty box twice, or a “life” will be lost and a new trial started.

3.10.3.4 VERBAL FLUENCY

This is a well established task of executive function¹³⁷, and a version taken from the Addenbrookes Cognitive Examination-Revised (ACE-R) was used¹⁶⁰. Participants are asked to generate as many words as they can beginning with the letter P in one minute, not including place or person names. They are then asked to generate as many types of animal they can in one minute, whose name begins with any letter of the alphabet. The total number of words generated for each category is converted to a score¹⁶⁰.

3.10.3.5 TRAIL MAKING TASKS A & B¹³⁸

This is a task of executive functioning. In Task A, participants are asked to connect a series of numbered circles on a piece of paper as quickly as possible. In Task B, participants are again asked to connect a series of circles containing ascending numbers or letters of the alphabet. On this occasion they are asked to alternate between numbers and letters (e.g. 1-A-2-B-3-C etc) and connect up all of the circles as quickly as possible. Prior to doing the task, participants are given short practice examples to complete. If an error is made, the examiner is allowed to point this out to the participant for them to correct. Each part is timed, and a time to completion for each part of the task is recorded. If the combined time is > 300s the task was discontinued¹⁶¹.

3.10.4 ATTENTION

3.10.4.1 SUSTAINED ATTENTION RESPONSE INHIBITION TASK (SART)¹⁶²

This is a test of sustained attention and response inhibition, originally designed for use with brain injured individuals. In this task single digit numbers are individually presented for 500ms on a computer screen. The font size and boldness of the digits varies, and a small cross is presented for 1000ms between digits. The participant has to press the space bar on the keyboard in response to every number presented on the screen, with one exception - they are told not to press the bar if the number 3 is presented. If they make an error and accidentally press the bar when a 3 is presented they are instructed to continue with the task as before. Fifty practice trials were completed followed by 270 test trials, lasting 405s in total. The number of commission errors (pressing bar when '3'

presented), omission errors (not pressing bar for all other numbers) and total errors was recorded for analysis.

3.10.5 FUNCTIONAL AND QUALITY OF LIFE ASSESSMENTS

3.10.5.1 INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL)¹⁶³

This is a questionnaire covering instrumental activities of daily living. A 15 point version was used that included 8 categories of instrumental ADLs and 7 basic ADLs. It is completed by the participant and carer to provide a score of functional impairment.

3.10.5.2 DEMENTIA QUALITY OF LIFE (DEMQOL)¹⁶⁴

This is a questionnaire covering how the participant has been feeling, how concerned they have been about aspects of their memory and about activities of daily living. It is scored out of 28 and used to give an overall score for perceived quality of life.

3.10.6 METACOGNITION

3.10.6.1 THE META-MEMORY IN ADULTHOOD QUESTIONNAIRE (MIA)¹⁶⁵

This is a questionnaire of 108 questions scored on a Likert scale. The questions are divided into 7 domains to give a measure of the participants' beliefs about their own memory function. The sub categories are strategy use, memory capacity, change in memory, tasks, locus, achievement, and anxiety. Total scores and scores broken down by sub category were analysed.

3.10.6.2 SUBJECTIVE REPORTS OF STRATEGY USE AND PERFORMANCE DURING SPAN TESTING

During the pre- and post-testing sessions, the span tasks were presented in two blocks, and participants were not informed which block consisted of structured or random trials. Immediately following each block of either structured or random trials, participants were asked:

- 1) Did you use any strategy to help you remember the numbers?

Based on their answer, participants were either coded to have explicitly used chunking strategies (score = 1), or not (score = 0).

After both blocks were administered participants were asked:

2) Did you find one of the blocks easier than the other and why, or did you find them the same?

Response to this question was coded 1-4 as follows:

1) participant found structured trials easier

2) participant found random trials easier

3) participant found no difference between blocks

4) no data available for participant (as these questions were administered following a revision to the study protocol to collect meta-cognitive data).

A 'match' score was also defined by whether the participant had a greater score on the trial type they had reported as easier (scored as 1= yes, 0 = no)

3.11 INTERVENTIONS

3.11.1 COGNITIVE TRAINING

Participants in the cognitive training group underwent 18 sessions of training on a structured digit span task. The quantity and intensity of training sessions was based on previous studies of successful cognitive training⁵³. Each session consisted of 30 trials of structured digit spans, divided into 2 blocks of 15 trials. Initially span length was 3 digits and the span length increased or decreased by one digit following a correct or incorrect response, as described in 3.9.1. At the beginning of the session participants were reminded that they may find it useful to group some digits together in 'chunks' according to the relationships between the numbers (e.g. 1-2-3 or 2-4-6) and that there would be deliberate structure within the spans to enable this. However, participants performed all the training trials independently and were not helped to identify chunks by the researcher during the trials. Three training lists of digit spans were used for the training sessions in a pseudo-random fashion. Each list consisted of 20 different combinations for each span length, and the span presented depended on how the participant had performed on the previous trial. Participants therefore were exposed to a range of structured stimuli during training, however most of the structure within the spans was a combination of digits consecutively increasing (1,2,3), decreasing (9,8,7), or increasing/decreasing by two (e.g. 2,4,6 or 9,7,5,3,1) or three (e.g. 9,6,3). The stimuli lists used in the testing sessions at pre- and post- were not used during training. Each training session took approximately 30 minutes. The digit spans were presented on a laptop computer at the participant's home. (Figure 3-8).

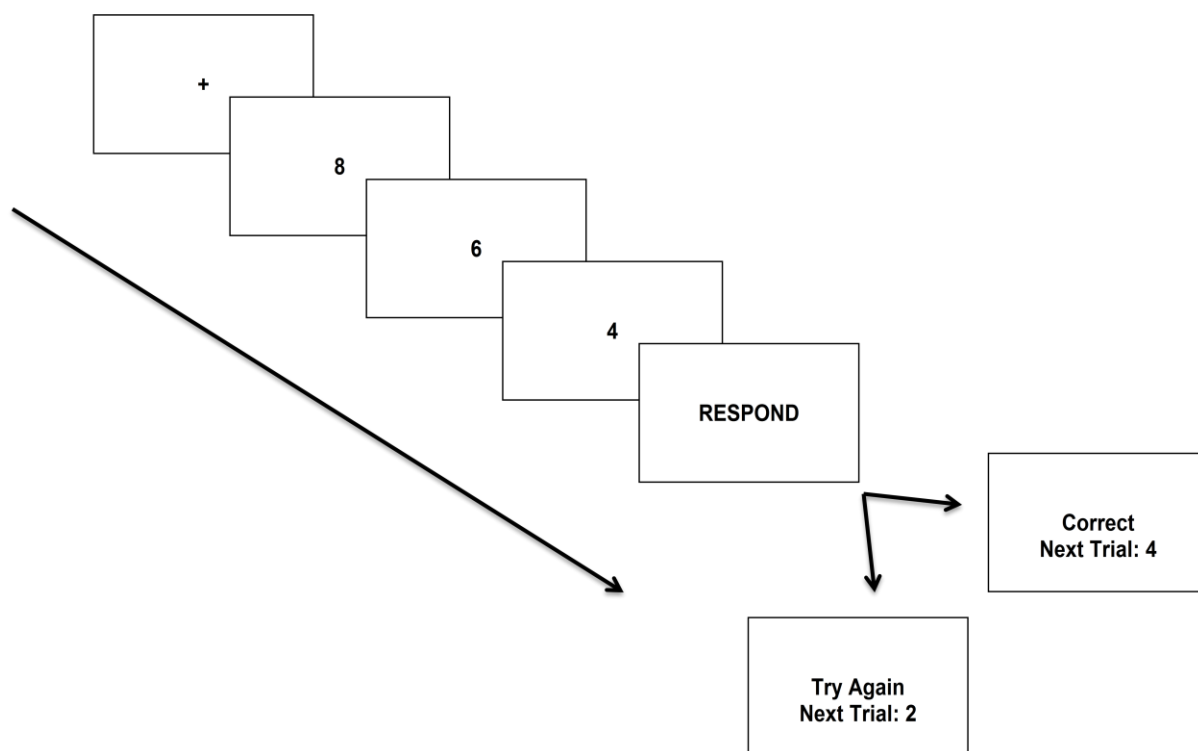


Figure 3-8: Schematic of the training intervention. Example demonstrates three structured digits, if the participant correctly recalls these digits in order; the subsequent trial will present four digits to be recalled.

3.11.2 CONTROL GROUP

Participants in the control group underwent 18 sessions of an attention control intervention. The same digit span program was used as in the training group, however participants performed 30 trials of a random 3 digit span, in two blocks of 15. At the end of each trial participants were informed if they had recalled the 3 digits correctly, however span length did not adjust according to correct/incorrect response, and remained fixed at 3 digits (Figure 3-9). A random number generator was used to produce the spans. Although the control intervention took slightly less time than the training, time was spent in general conversation and each session lasted approximately 30 minutes.

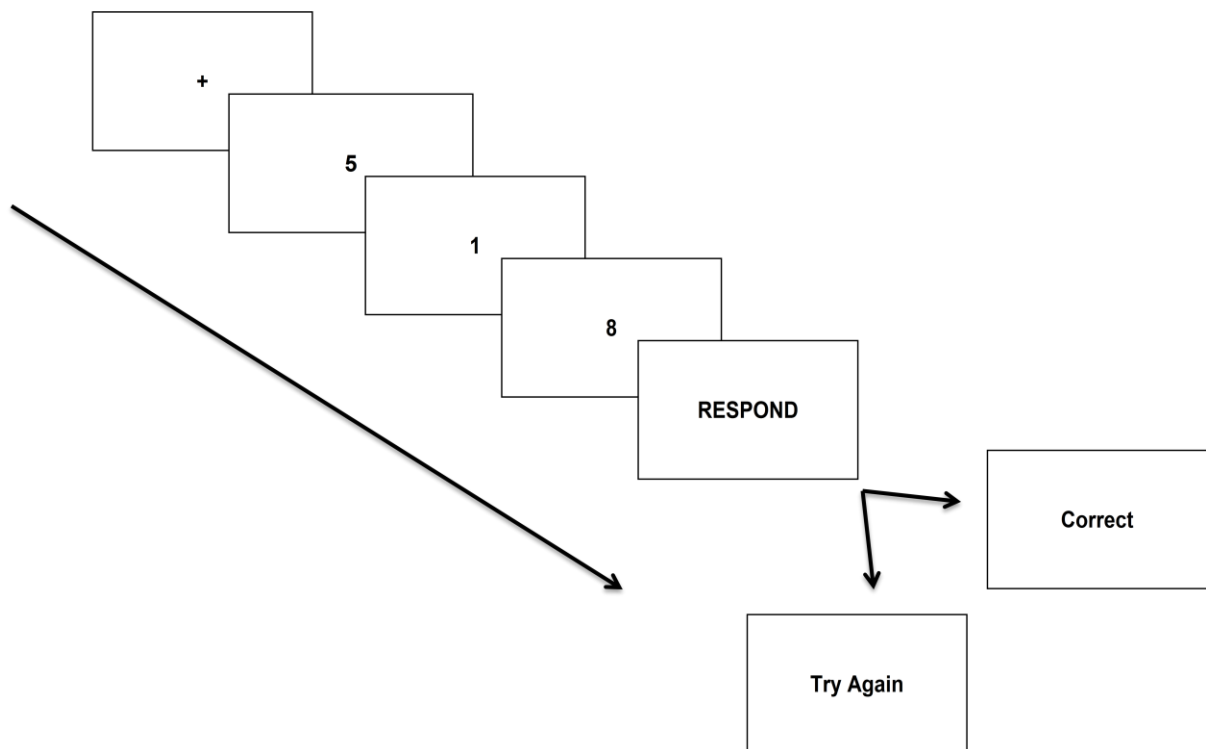
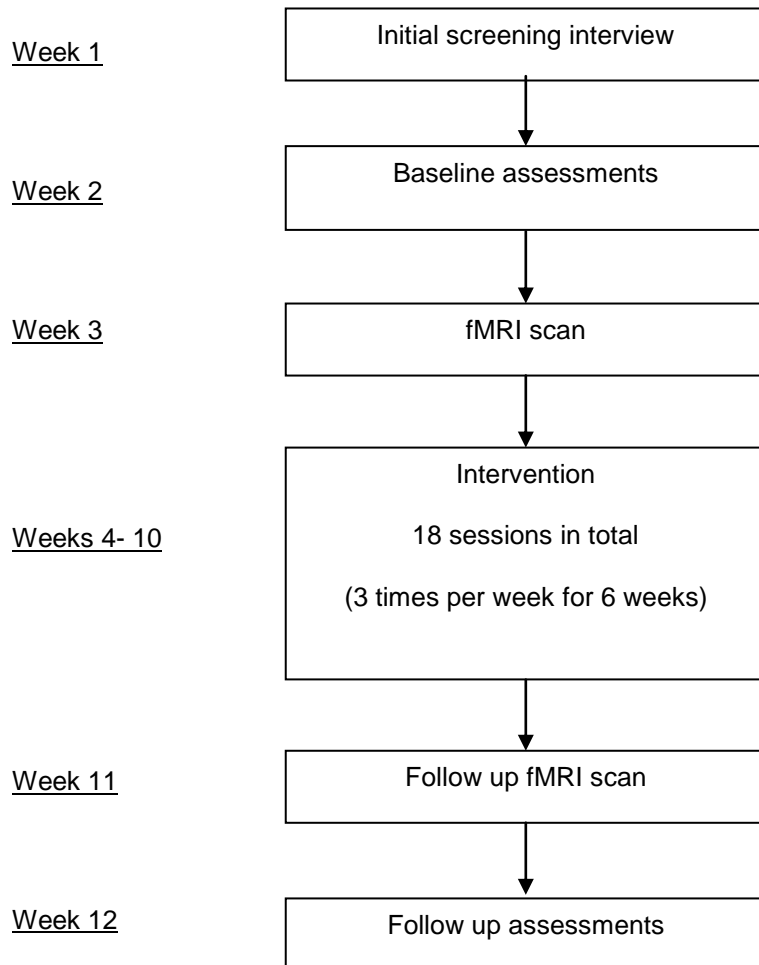


Figure 3-9: Schematic of the control intervention.

Example demonstrates three random digits, All trials presented during control intervention consisted of three random digits, irrespective of whether they were correctly recalled.

3.12 SUMMARY OF PARTICIPANT'S INVOLVEMENT

Prior to commencing study: Review of medical records to confirmation eligibility



There were therefore a total of approximately 22 home visits, and 2 fMRI scans at the Centre for Neuroimaging studies, IOP, per participant, over approximately 12 weeks.

3.13 STATISTICAL ANALYSES

For the primary outcome measures, mean span accuracy scores were analysed using a mixed repeated measures analysis of variance (ANOVA) in statistical Package for the Social Sciences (SPSS v 22.0)¹⁶⁶.

For the secondary outcome measures, maximum scores on the MMSE, ADAS Cog, Grammatical reasoning, Odd One Out, Paired Associate learning, Self Ordered Search, Logical memory I and II,

IADL, DEMQoL, verbal fluency score, time to completion for Trail making task A&B, sub scores and total scores on the MIA and commission errors, omission errors and overall errors in the SART were all analysed using mixed repeated measures ANOVAs in SPSS v 22.0. Where appropriate, all tasks within the same cognitive domain were included in an initial repeated measure ANOVA to examine for overall effects, with subsequent ANOVAs examining each task independently. Assumptions of parametric data were assessed for all data. The assumption of normality was assessed by plotting histograms and Q-Q plots of the raw data or residuals. Values of skewness, kurtosis and the Kolmogorov-Smirnov test were also used to test for normal distribution of the data. Homogeneity of variance was assessed using the Levene statistic. If the assumptions of parametric data were violated, Mann-Whitney and Wilcoxon signed-rank non parametric tests were conducted. For all analyses the α significance level was set at 0.05. Correction for multiple testing due to the number of neuropsychological tasks was not performed, as power calculations were based on an α value of 0.05. The issue of multiple testing is addressed in the discussion, (section 7.11.5).

3.14 SAMPLE SIZE

As the study was based on an fMRI paradigm, the sample size was calculated from previous studies using a similar paradigm, yielding significant results in healthy controls with group sizes of $n = 14$, producing effect sizes of 0.9 and 1.7^{24 26}. Recent cognitive training studies have yielded significant results in controls with group sizes of $n = 8$ producing an effect size of 1.75⁵³. Based on these studies, power calculations give 80% power to detect a significant difference ($p < 0.05$) with group sizes of > 12 .

3.15 ETHICAL APPROVAL AND TRIAL REGISTRATION

The study was reviewed and approved by the NRES Committee East of England-Cambridge East (REC reference number 10/H0304/68).

Prior to commencing the study, the trial was registered and issued with the International Standard Randomised Controlled Trial Number: ISRCTN43007027.

Chapter 4 METHODS - NEUROIMAGING

4.1 BEHAVIOURAL FMRI TASK

Participants underwent two structural and fMRI examinations, at baseline and then post intervention. The fMRI cognitive activation protocol was based on a digit span paradigm performed by healthy young individuals²⁶ and adapted for use in patients with AD.

The same digit span task was presented during each FMRI session (Figure 4-1). This task was a variation of the digit span task administered during both the training and control interventions. Five digits were successively presented on a screen. Participants were instructed to remember the digits in order, and when the word 'recall' appeared on the screen, to say the numbers back out loud, in the correct order. The words 'confident' and 'not confident' were then presented on the screen, and participants were asked to state if they were confident or not that they had recalled the numbers correctly. Twenty trials were presented per run, with structured and random sequences presented pseudo randomly. In total three runs of twenty trials were presented per scanning session.

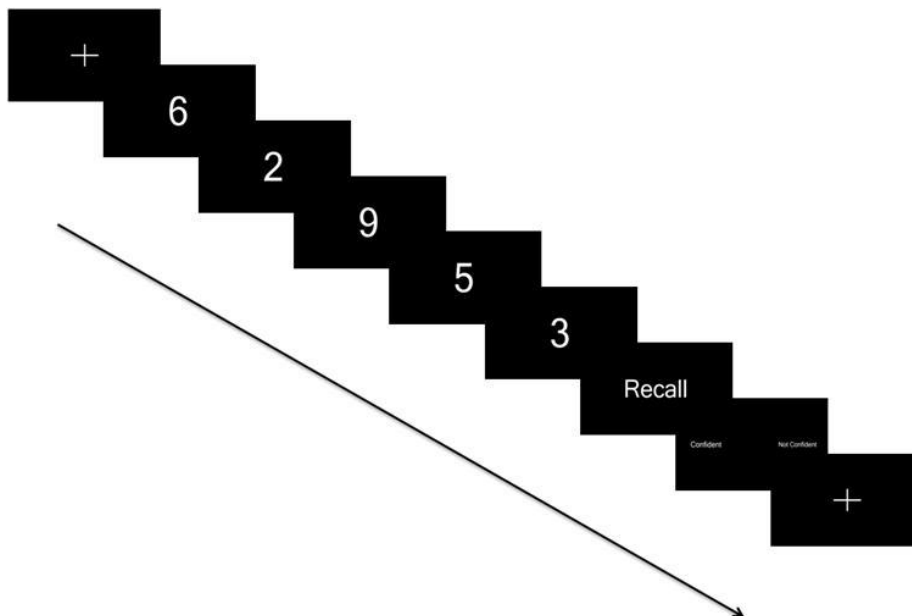


Figure 4-1 Schematic of digit span task performed by participants during fMRI scanning. A random trial is shown.

4.1.1 FMRI TASK TIMING

The order and duration of events during the fMRI task is shown in Table 4-1.

EVENT	DURATION (ms)
PRE-TRIAL FIXATION CROSS	500
FIRST DIGIT DISPLAY	1000
INTERDIGIT INTERVAL	500
SECOND DIGIT DISPLAY	1000
INTERDIGIT INTERVAL	500
THIRD DIGIT DISPLAY	1000
INTERDIGIT INTERVAL	500
FOURTH DIGIT DISPLAY	1000
INTERDIGIT INTERVAL	500
FIFTH DIGIT DISPLAY	1000
INTERDIGIT DISPLAY	500
PRE- RECALL DELAY	VARIABLE (2000- 5000ms)
RECALL PROMPT	7000
CONFIDENCE PROMPT	3000
POST- FIXATION CROSS	500ms
POST- TRIAL DELAY	VARIABLE (4000-10000ms)

Table 4-1: Order and duration of events during fMRI task.

The pre-recall delay and post-trial delay varied between trials, however the durations were fixed for each trial, and therefore all participants had identical timings for each functional run. The first functional run was 584.05s, the second, 594.035s and the third, 588.022s in duration.

4.1.2 PRACTICE AND PARTICIPANT MONITORING DURING FMRI

All participants had a training session prior to the FMRI scan to ensure they could understand and perform the task. Participants also practiced the task using a mock MRI scanner, in order to familiarise themselves with the environment and experience of MRI prior to the scan session.

Participants were informed that they would be able to communicate with the radiographers and researcher via a microphone and headphones at any time during the scan. They also held a buzzer button and it was stressed that if they were uncomfortable, or wished to terminate the scan they could communicate this either by pressing the buzzer or speaking directly to the researcher via the microphone. The scan session was divided into a series of structural and functional scans, and the participant was asked about their comfort and willingness to continue between each of the scans to ensure the experience was as comfortable as possible. Total scan time was approximately 75 minutes.

4.2 FMRI PROTOCOL.

4.2.1 FUNCTIONAL PARAMETERS AND DATA ACQUISITION

Both pre- and post- intervention fMRI scans were performed on the same Siemens 3T scanner at the Centre for Neuroimaging Sciences, Institute of Psychiatry. An 8 channel head coil was used.

The order of scans is shown in Table 4-2:

	Scan	Duration (mins)
1)	3 plane localiser	< 1:00
2)	Axial scan 36 slices	< 1:00
3)	Sagittal MP-RAGE structural scan	10:04
4)	Axial high resolution GE- 43 slices	2:00
5)	First functional run- Digit span 1	10:09
6)	Axial T2 Propeller- 26 slices angled along AC/PC line	2:45
7)	Second functional run- Digit span 2	10:09
8)	Axial T2 Propeller Flair	3:20
9)	Third functional run- Digit span 3	10:09

Table 4-2: Order of scans during each session.

For all functional runs, an echo planar imaging (EPI), event related design was used. 37 slices covering the whole head were taken per repetition time (TR), with a slice thickness of 3mm and gap of 0.3mm. The field of volume was 21.1, such that voxel size was an isotropic 3.3mm^3 . The TR was 2 seconds and the echo time (TE) was 30ms. The flip angle was 75 degrees. 4 dummy scans were acquired and discarded and 300 images were taken per location with a total of 11100 images taken per functional run.

The participants' verbal responses were documented in real time by the researcher and also automatically recorded in both filtered and unfiltered audio files. The onset times of each event and volume times were also automatically recorded. Pulse oximetry data (pulse and respiratory rate) was collected for all participants.

4.3 FMRI ANALYSIS- PRE-PROCESSING

All pre-processing and analysis was conducted using SPM8 software ¹⁶⁷.

4.3.1 RESETTING THE ORIGIN

During data acquisition the origin was set as the centre of the scanner, however to improve the quality of registration the origin was reset to the location of the anterior commissure (AC). Each participant's MPAGE structural image and first functional image were manually reset to the AC, and all other functional images were re-oriented to this image for all 3 playlists per scanning session, using the display function within SPM8. This increases the likelihood of the optimal global solution being found when the images are warped to template space, and therefore improves the quality of co-registration.

4.3.2 CREATING A DARTEL TEMPLATE

The DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra)¹⁶⁸ toolbox within SPM8¹⁶⁷ was used to create a group average structural template for normalisation. During the normalisation process images are transformed and warped into a standardised brain in MNI space. However as all the participants were elderly AD patients, it is likely that their brains would be structurally different from the standardised healthy brain templates. Therefore by using DARTEL, a study-specific average template was produced to improve inter-participant alignment and more accurate localization for analysis. DARTEL registers images by computing a single flow-field that stores deformation information for each participant. New tissue class images were generated and iteratively matched to a template generated from their own mean. 'Smoothed' spatially normalised images were then generated aligned to MNI space.

This procedure was conducted separately for both pre- and post-MPAGE structural images for each participant.

4.3.3 QUALITY ASSESSMENT

The time series difference analysis (TSDiffAna) program was used to review the variance between the images in each fMRI scanning session¹⁶⁹. The aim was to check the images for quality and highlight any images where there was a peak in variance due to movement or scanner artefact.

Output graphs were produced displaying the variance between images, slices, max/min/mean slice variance and mean voxel intensity.

These graphs were used to assess the amount of variance in the time series and specifically to identify any spikes of increased variance. Any peaks or spikes in variance may represent artefact, due to technical issues with the scanner or significant movement artefact.

It was anticipated that there may be considerable movement artefact in an AD patient group. A priori, it was decided that variance would be acceptable if the scaled and slice by slice variance was <300, and the mean voxel intensity was between 0.9 - 1.1.

Where there were spikes of increased variance outside these limits, the associated images were cross-referenced with the movement parameter graphic outputs from SPM and checked by viewing the images using the CheckReg function in SPM8¹⁶⁷. Artefact was reviewed with the lead MRI physicist for the study and it was agreed that movement rather than scanner error was the most likely cause of the artefacts seen. Excessive movement was managed during first-level analysis (see section 4.4.1). See Appendix 2 for examples of TSDiffAna output graphs.

4.3.4 PRE-PROCESSING

A batch script was used for pre-processing containing the following steps:

4.3.5 SLICE TIMING

All images were corrected for slice timing as data had been collected as 37 interleaved slices, with an interscan interval (TR) of 2 seconds. Slice 2 (the mid-slice) was used as the reference slice.

4.3.6 REALIGNMENT

All functional images were realigned and corrected for motion using a series of rigid translations on, and rotations around, x-, y- and z-axes. All slice timing corrected images from each functional run were realigned and the mean image was resliced. The default settings in SPM8 for realignment estimation were used (Quality: 0.9, Separation: 4, Smoothing (FWHM): 5, Num Passes: Register to mean, Interpolation 2nd Degree B-Spline, Wrapping: No wrap, Weighting: 0 files)³⁴. Plots of motion parameters in each direction (x, y, z) and rotation (pitch, yaw, roll) were produced for each participant.

These motion parameters were then included in the design matrix as regressors of no interest (see below).

4.3.7 CO-REGISTRATION

The functional images were then co-registered to the structural reference image. The reference image was the participant's structural MPAGE image. The mean image produced by the realignment step was used as the source image (i.e. moved to best match the reference image), and all other slice-corrected images from all three functional runs were selected to remain in alignment with the source image.

Estimation options were kept as the default settings in SPM8 (Objective Function Mutual information, Separation [4 2], Tolerances 1 x 12 double, Histogram Smoothing [7 7])³⁴.

4.3.8 NORMALISATION TO MNI SPACE

The co-registered images were then normalised to MNI space using the group specific DARTEL template and participant-specific flow-field parameters. A 2 x 3 double bounding box was used and images were smoothed using an 8 x 8 x 8 Gaussian kernel³⁴.

All pre-processed functional images were then compared to the EPI template in SPM8 to check the quality of the pre-processing results.

4.4 FMRI ANALYSIS- FIRST LEVEL ANALYSES

Within-participant analysis was conducted for two levels of events.

- 1) Basic analysis of all trials
- 2) Main analysis of only correct trials and confidence reports

4.4.1 BASIC MODEL

The basic analysis extracted the onset and durations from all trials and examined four conditions:

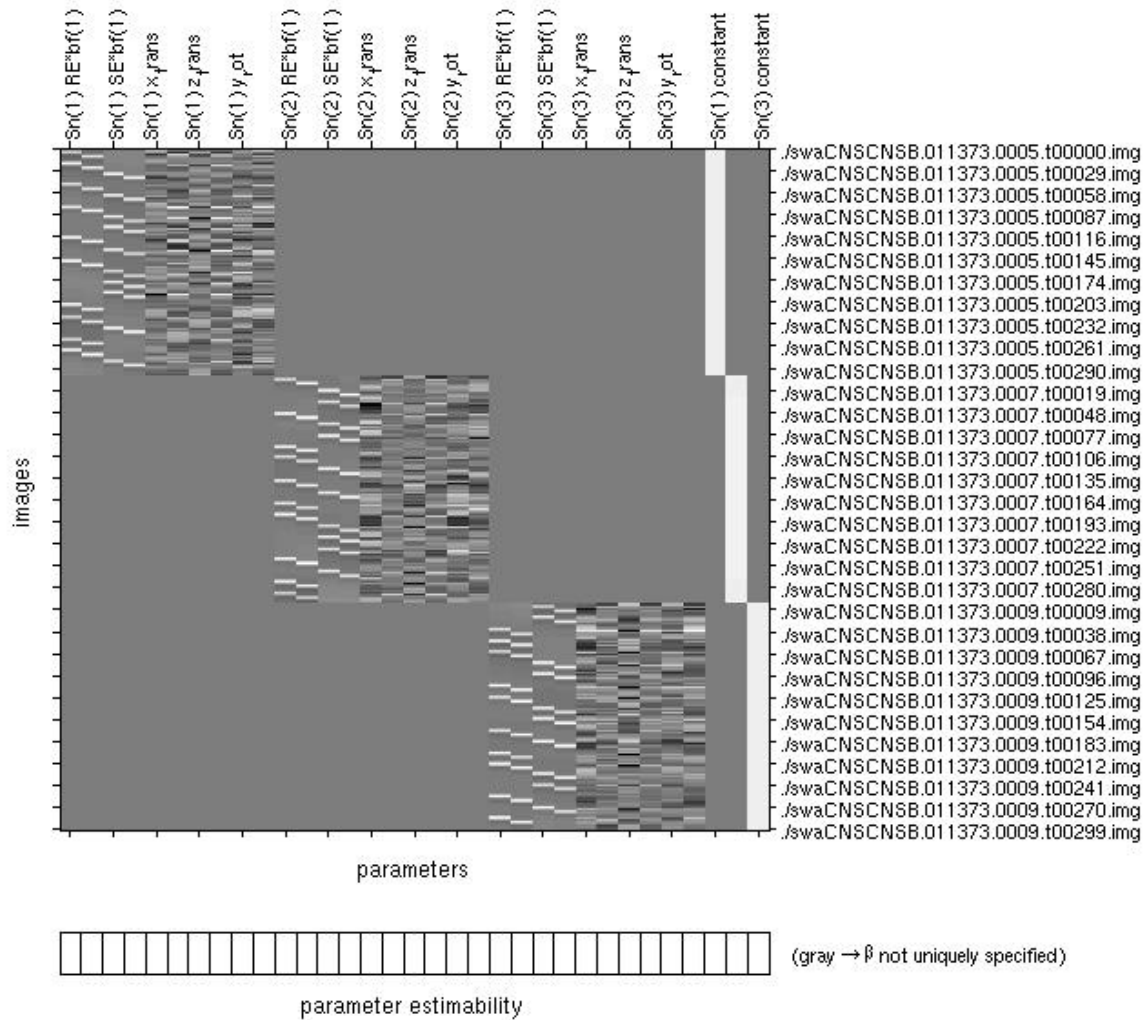
- 1) Random trials- encoding event (RE)
- 2) Random trials- recall event (RR)
- 3) Structured trials- encoding event (SE)
- 4) Structured trials- recall event (SR)

All trials were used in this analysis, irrespective of whether the participant gave the correct response. Therefore, as all participants received identical stimulus lists during the pre- and post- trial fMRI session, the onsets and durations of these events were identical for all participants.

The exception was for participants who had scanning sessions terminated early for various reasons (such as requesting early termination of the session). In these cases, only the onsets and durations of trials actually performed were analysed, with the onset and duration lists corrected to reflect this for these participants.

The design matrix was formed from the 4 specified event regressors of interest (random encoding, random recall, structured encoding, structured recall) and six movement regressors, each corresponding to 3 transformations (x, y, z) and 3 rotations (pitch, roll, yaw) produced from the realignment stage of pre-processing. If there was excessive movement between subsequent images, resulting in significant movement artefact on the images, these were excluded from analysis by defining them as additional regressors of no interest. This was done by calculating the difference between the translation and rotation values between all adjacent images and producing a value for movement between images. If this value was greater than 4mm in any direction of translation, or 0.1 radians in any direction of rotation then the image was excluded. The design matrix is shown in Figure 4-2.

Statistical analysis: Design



Design description...

Basis functions : hrf
Number of sessions : 3
Trials per session : 4 4 4
Interscan interval : 2.00 {s}
High pass Filter : Cutoff: 180 {s}
Global calculation : mean voxel value
Grand mean scaling : session specific
Global normalisation : None

Figure 4-2: Design matrix for basic analysis.

The haemodynamic response was convolved with the specified time series of events at each voxel using the General Linear model, and low-frequency noise was removed using a high pass filter. The relative contribution (β) of each variable (X) in the design matrix to the observed data (Y) at each voxel was estimated using the general linear model, where $Y = X\beta + \text{error}$.

4.4.1.1 CONTRASTS:

Once the design matrices had been defined and estimated, the following contrasts for the first-level analysis were specified:

contrast 1= structured trials during encoding

contrast 2= random trials during encoding

contrast 3= all trials (structured and random) during encoding

contrast 4= structured trials encoding > random trials during encoding

contrast 5= random trials encoding > structured trials during encoding

contrast 6= all trials during recall

If extra regressors were created for participants in the first-level specification, these were accounted for by adjusting the contrasts so they contained the correct number of parameters. This was also the case for participants who had only one or two functional runs.

The β values for each contrast were then entered into T-tests to examine for significant effects at an individual session level, and the structured and random contrasts were taken to the second-level group analysis.

4.5 MAIN ANALYSIS MODEL

In this model, only correct trials were examined, and encoding, delay and recall events were included in the model. Incorrect and 'not confident' responses were also modelled as regressors of no interest.

4.5.1 EXTRACTING ONSET AND DURATIONS

Behavioural data during each participant's scanning session was examined, and participant specific onset and duration timings were extracted for the following events:

1. Correct random trials
2. Correct structured trials
3. Incorrect random trials
4. Incorrect structured trials
5. Correct trials with confident response
6. Incorrect trials with confident response
7. Correct trials with not confident response
8. Incorrect trials with not confident response

For each of these conditions, the following data was extracted in separate text files:

Text file 1 = Encoding onset (fixed duration 7.5s for all trials)

Text file 2 = Delay (pre- recall delay) onset

Text file 3 = Delay durations (variable duration)

Text file 4 = Recall onset (fixed duration 7s for all trials)

Text file 5 = Confidence response onset (fixed duration 3s for all trials)

Text file 6 = Post- trial delay onset

Text file 7 = Post- trial delay duration (variable duration)

Therefore there were $8 \times 7 = 56$ text files produced per functional digit span run. As three runs were conducted per scanning session, a total of $3 \times 56 = 168$ text files containing individual onset or duration data were produced per participant per scanning session. These text files were produced using a Visual Basic macro in Microsoft Excel.

4.5.2 DEFINING REGRESSORS

In order to capture the regressors of interest - namely correct random trials, correct structured trials and confident correct trials, at the encoding, delay and recall time points, the events were parameterized to ensure events modelled were independent (orthogonal).

Four parameters were modelled for each of the encoding, delay and recall phases, with 12 parameters overall in each functional run.

- 1) All random trials (correct and incorrect trials)
- 2) All structured trials (correct and incorrect trials)
- 3) All not confident trials (correct and incorrect trials)
- 4) All incorrect trials (structured and random trials)

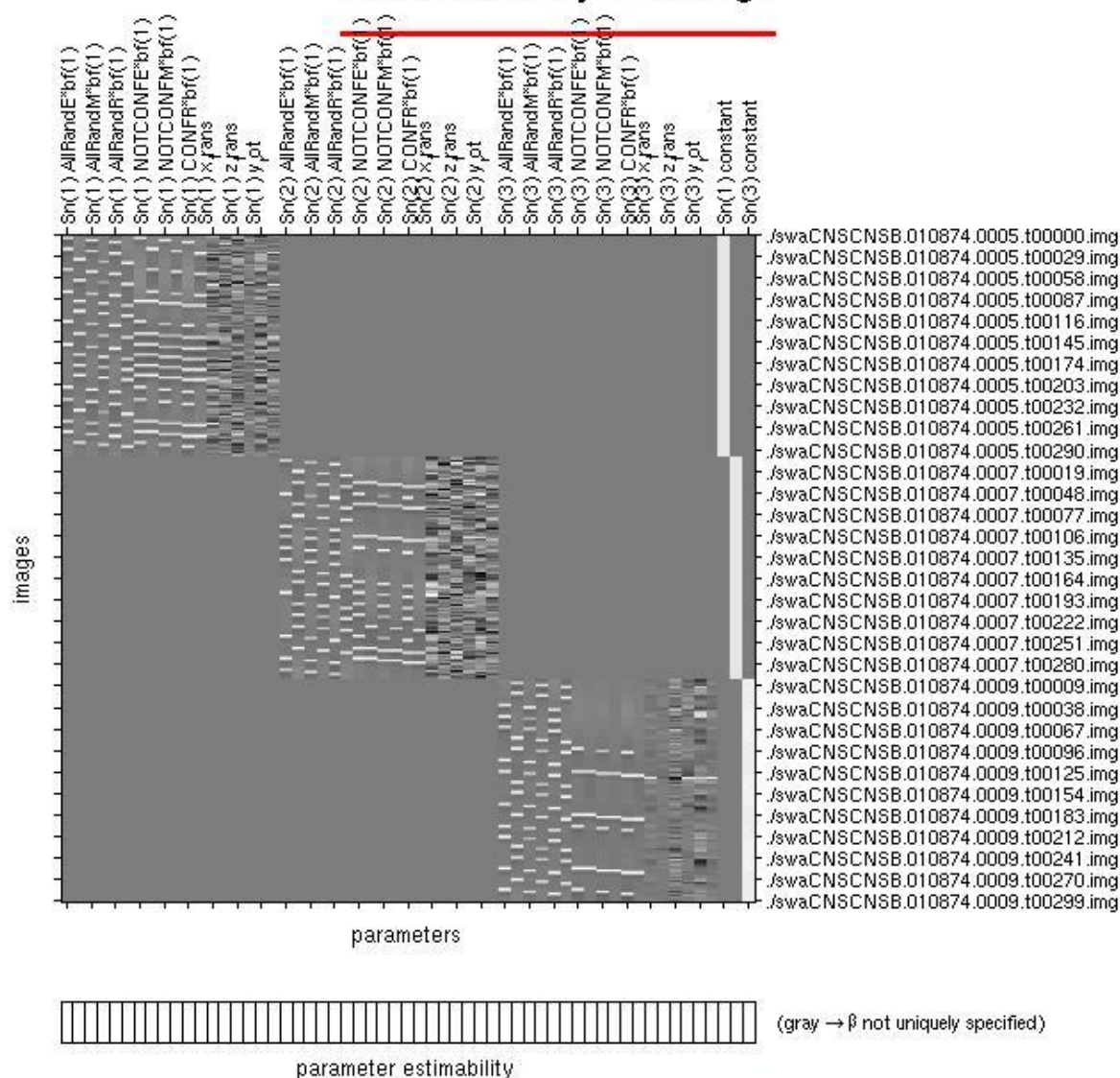
In this way, the random and structured parameters modelled only correct and confident trials, as parameters 7-12 modelled out all incorrect and non confident trials.

In addition, the 6 movement parameters from realignment were included as regressors of no interest. As for the basic model, extra movement regressors were created if a translation between successive images was $> 4\text{mm}$ or rotation between successive images was > 0.1 radians.

If no conditions were present (e.g. there were no incorrect trials) a value of '1' with zero duration at time point zero was placed in the initial image for that regressor, and that participant would be excluded from analysis for contrasts where parameters were not unique.

Using the general linear model (GLM), β values were estimated for each of the defined variables, and by including separate incorrect and non confident regressors, the effect of incorrect and not confident trials were modelled out of the combined correct and incorrect structured and random regressors. The design matrix is shown in Figure 4-3. A batch script was used to conduct the first-level analysis (see Appendix 3 for code).

Statistical analysis: Design



Design description...

Basis functions : hrf
Number of sessions : 3
Trials per session : 12 12 12
Interscan interval : 2.00 {s}
High pass Filter : Cutoff: 180 {s}
Global calculation : mean voxel value
Grand mean scaling : session specific
Global normalisation : None

Figure 4-3: Design matrix for main analysis

4.5.3 DEFINING CONTRASTS

To analyse the different trial types and confidence responses, twenty-one contrasts were then defined for all participants. These were seven contrasts defined for each of the encoding, delay and recall phases of the task:

- 1) Random trials
- 2) Structured trials
- 3) All trials (structured and random)
- 4) Structured trials > random trials
- 5) Random trials > structured trials
- 6) Not confident trials
- 7) Incorrect trials

If additional movement regressors or reduced number of runs were present, then the contrasts were adapted accordingly. See Appendix 3 for code and details of the defined contrasts.

4.6 FIRST-LEVEL RESULTS

At the individual participant level the following contrasts were examined;

- 1) Effect of encoding (all trials) vs baseline
- 2) Effect of delay (all trials) vs baseline
- 3) Effect of recall (all trials) vs baseline.
- 4) Effect of chunking (str>rand and rand>str contrasts)

T- tests were used to examine activations and deactivations with the first three contrasts. These were performed to identify whether the working memory task produced the expected areas of brain activation, and therefore to demonstrate that the digit span paradigm was successfully reflecting task performance. The effect of chunking during encoding and delay was also examined using a liberal significance threshold.

4.7 SECOND-LEVEL ANALYSIS

4.7.1 DESIGN MATRIX

Group statistical analyses were conducted using random effects analysis to examine the consistency of effect sizes across the group.

The individual estimated β values from the first-level analysis for structured trials vs baseline and random trials vs baseline were taken to the second-level analysis and a factorial design was employed for the group analysis.

The factorial design had two dependent within participants factors: TIME (pre- vs post-), and TRIAL TYPE (structured vs random), and one independent between participants factor: GROUP (control vs training). A 2 X 2 X 2 Factorial design was therefore produced with the following eight factors:

1 1 1 = STRUCTURED TRIALS IN CONTROL PARTICIPANTS AT BASELINE (PRE)

1 1 2 = RANDOM TRIALS IN CONTROL PARTICIPANTS AT BASELINE (PRE)

1 2 1 = STRUCTURED TRIALS IN TRAINING PARTICIPANTS AT BASELINE (PRE)

1 2 2 = RANDOM TRIALS IN TRAINING PARTICIPANTS AT BASELINE (PRE)

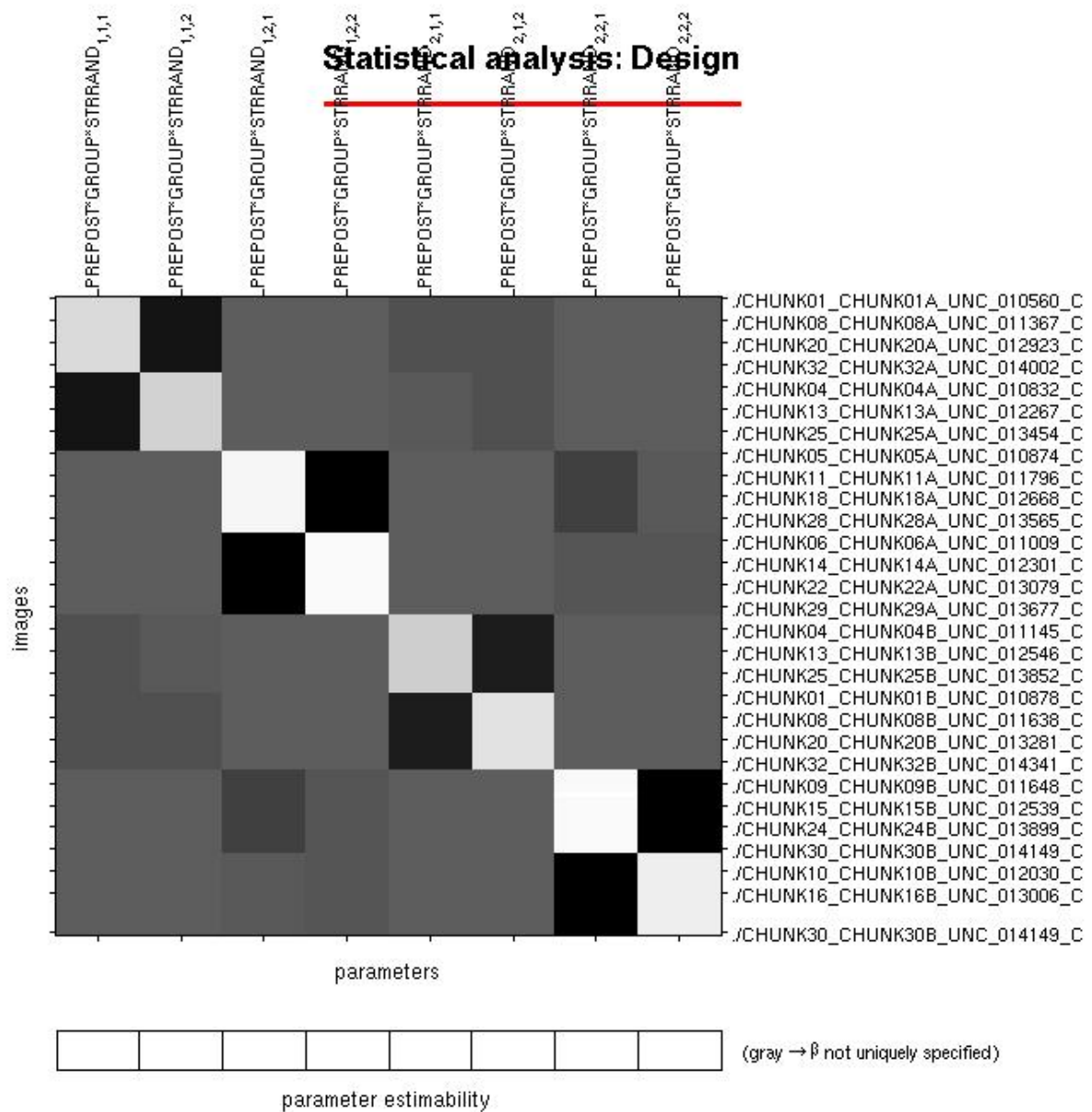
2 1 1 = STRUCTURED TRIALS IN CONTROL PARTICIPANTS AT FOLLOW-UP (POST)

2 1 2 = RANDOM TRIALS IN CONTROL PARTICIPANTS AT FOLLOW-UP (POST)

2 2 1 = STRUCTURED TRIALS IN TRAINING PARTICIPANTS AT FOLLOW-UP (POST)

2 2 2 = RANDOM TRIALS IN CONTROL PARTICIPANTS AT FOLLOW-UP (POST)

The full factorial design matrix is shown in Figure 4-4.



Design description...

Design : Full factorial
Global calculation : omit
Grand mean scaling : <no grand Mean scaling>
Global normalisation : <no global normalisation>
Parameters : 8 condition, +0 covariate, +0 block, +0 nuisance
 8 total, having 8 degrees of freedom
 leaving 108 degrees of freedom from 116 images

Figure 4-4: Full factorial design for second-level analysis

4.7.2 REGION OF INTEREST (ROI) ANALYSIS

In previous fMRI studies of verbal digit span performance on structured and random spans, differences in activation were found primarily in the dorsolateral prefrontal cortices (DLPFC) and posterior parietal cortices (PPC)^{24 26}.

The *a priori* hypothesis, as stated when the trial was registered (ISRCTN43007027) was therefore that chunking training would result in changes of activation in bilateral DLPFC and PPC. Due to differences in anatomy between young healthy participants and an AD population, the positive effect of task contrast generated by the study group was used to find orthogonal regions of interest.

The MarsBar toolbox in SPM8¹⁷⁰ was used to define a 10mm sphere around the ROI coordinates.

The β values were then extracted and repeated measures analyses of variance (ANOVAs) were conducted in SPSS vs 22.0¹⁶⁶ to examine for main effects and interactions. Assumptions of parametric data were assessed for all data extracted from MarsBar using histograms and Q-Q plots of the residuals, the Kolmogorov-Smirnov test and Levene's test. If the assumptions of normality or homogeneity of variance were violated, the data was examined and winsorized, replacing any value greater or less than the mean \pm 2.5 x SD, with the exact values of the mean \pm 2.5 x SD. The tests for normality and homogeneity of variance were then repeated. Non winsorized data was also analysed as part of the sensitivity analysis.

The main analyses of interest were:

- 1) Positive effect of task – to examine overall activation due to the performance of the task
- 2) Main effect of time (pre- vs post-) (F contrast): to examine overall effects due to the time interval between scans
- 3) Main effect of structured vs random trial type (F contrast): to examine overall effects of chunking
- 4) Interaction of time x group (F contrast): to examine any overall effects of the training intervention.
- 5) Interaction of time, trial type and group, to examine any differential effects of training when performing structured or random trials

The above analyses were conducted for encoding and delay events.

Whole brain analysis was then conducted to examine for significant areas of activation or deactivation other than in the defined ROIs.

4.8 VOXEL BASED MORPHOLOGY

Voxel based morphology (VBM) was conducted to examine for significant structural differences between the groups, and whether training resulted in any structural differences.

4.8.1 PRE-PROCESSING

24 participants had MP-RAGE images at both pre- and post- time points. 3 participants had only MP-RAGE images at baseline, two had only MP-RAGE images at follow-up and one participant had no suitable structural images for analysis.

Pre- and post-intervention MP-RAGE images were pre-processed separately using the DARTEL toolbox in SPM8. As described above in 4.3.1, the origin of each structural image was reset to the AC. One participant was excluded at this stage due to excessive movement artefact on the follow-up image. Therefore 12 control and 11 training participants were included in the VBM analysis.

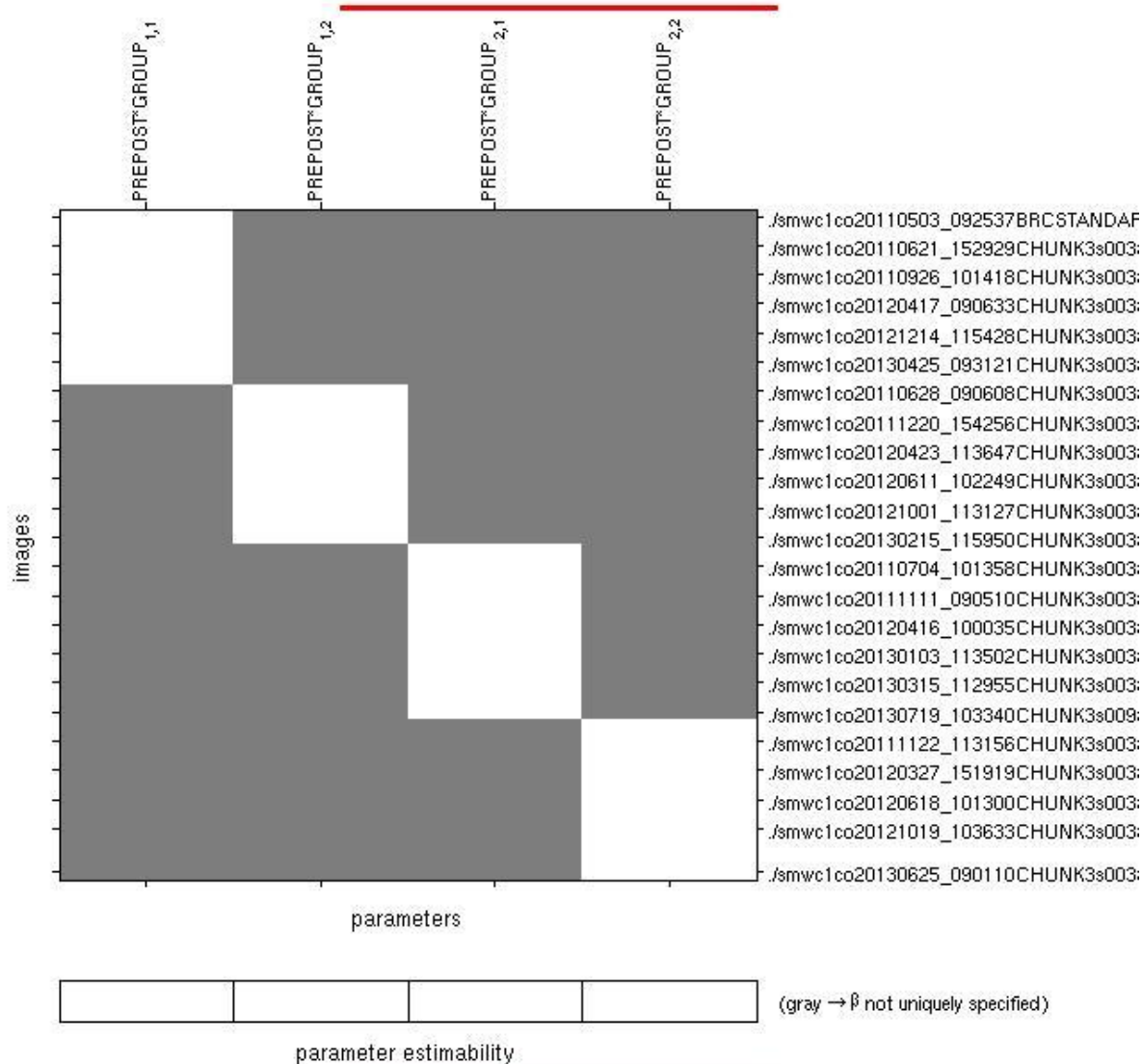
4.8.2 CREATING A DARTEL TEMPLATE

The DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra) toolbox within SPM8¹⁶⁸ was used to create a group average structural template for the normalisation step. As described above, the DARTEL toolbox was used to compute a single flow-field storing deformation information for each participant. New tissue class images were generated and iteratively matched to a template generated from their own mean. 'Smoothed' spatially normalised images were then generated aligned to MNI space. This procedure was completed for both the pre- and post- MP-RAGE structural images for each participant.

4.8.3 VBM ANALYSIS

Analysis of the main volumes of interest (VOI) defined for functional analysis along with whole brain analysis was performed. A factorial design was used with time (pre- vs post-training) as a dependent factor and group (control vs training) as an independent factor. Threshold masking was done using the default in SPM8 of 0.2 and no global normalisation was conducted¹⁷¹. The design matrix is shown in Figure 4-5. Analysis was then conducted at a whole brain level to identify significant time x group interactions and also at a VOI level using defined VOI from the functional analysis.

Statistical analysis: Design



Design description...

Design : Full factorial
Global calculation : omit
Grand mean scaling : <no grand Mean scaling>
Global normalisation : <no global normalisation>
Parameters : 4 condition, +0 covariate, +0 block, +0 nuisance
 4 total, having 4 degrees of freedom
 leaving 42 degrees of freedom from 46 images

Figure 4-5: VBM factorial design.

4.9 PSYCHO-PHYSIOLOGICAL INTERACTIONS

Psycho-physiological interactions (PPI) allow examination of functional connectivity between brain regions¹⁷². As previous studies had implicated bilateral DLPFC and PPC regions during chunking²⁶, PPI analysis was used to assess for evidence of functional connectivity between the RDLPFC and LDLPFC, LPC and RPC regions. PPI estimates the correlation in activity between two regions over time and examines if these interactions between regions differ with a psychological variable. Evidence of functional connectivity between two regions is provided if the time course correlations change in synchrony with the psychological variable. Interaction regressors are estimated from the task and blood oxygen level dependent (BOLD) time courses using the GLM and can then be analysed for main effects and interactions between the events of interest¹⁷³.

4.9.1 PPI DESIGN

For the PPI analysis, data from the basic model (all trials opposed to only correct trials) was examined. The seed region was taken from the RDLPFC ROI. The other ROIs were then included as ROIs to examine PPIs between the RDLPFC and LDLPFC, LPC and RPC.

Regressors for physiological response (BOLD response) and psychological task were used to produce an interaction regressor (PPI) between the seed region and each ROI (Figure 4-6).

The design matrix is shown in Figure 4-7.

Contrasts were then produced to examine

- 1) Structured trials during encoding
- 2) Random trials during encoding

As in the functional analysis, if participants had less than three functional runs, or additional movement regressors, these were accounted for in the contrasts.

The interaction regressors were then extracted into SPSS for structured and random trials at each time point (pre- and post-) and a repeated measures ANOVA was conducted for each ROI to examine main effects and interactions of time, trial type and group using SPSS.

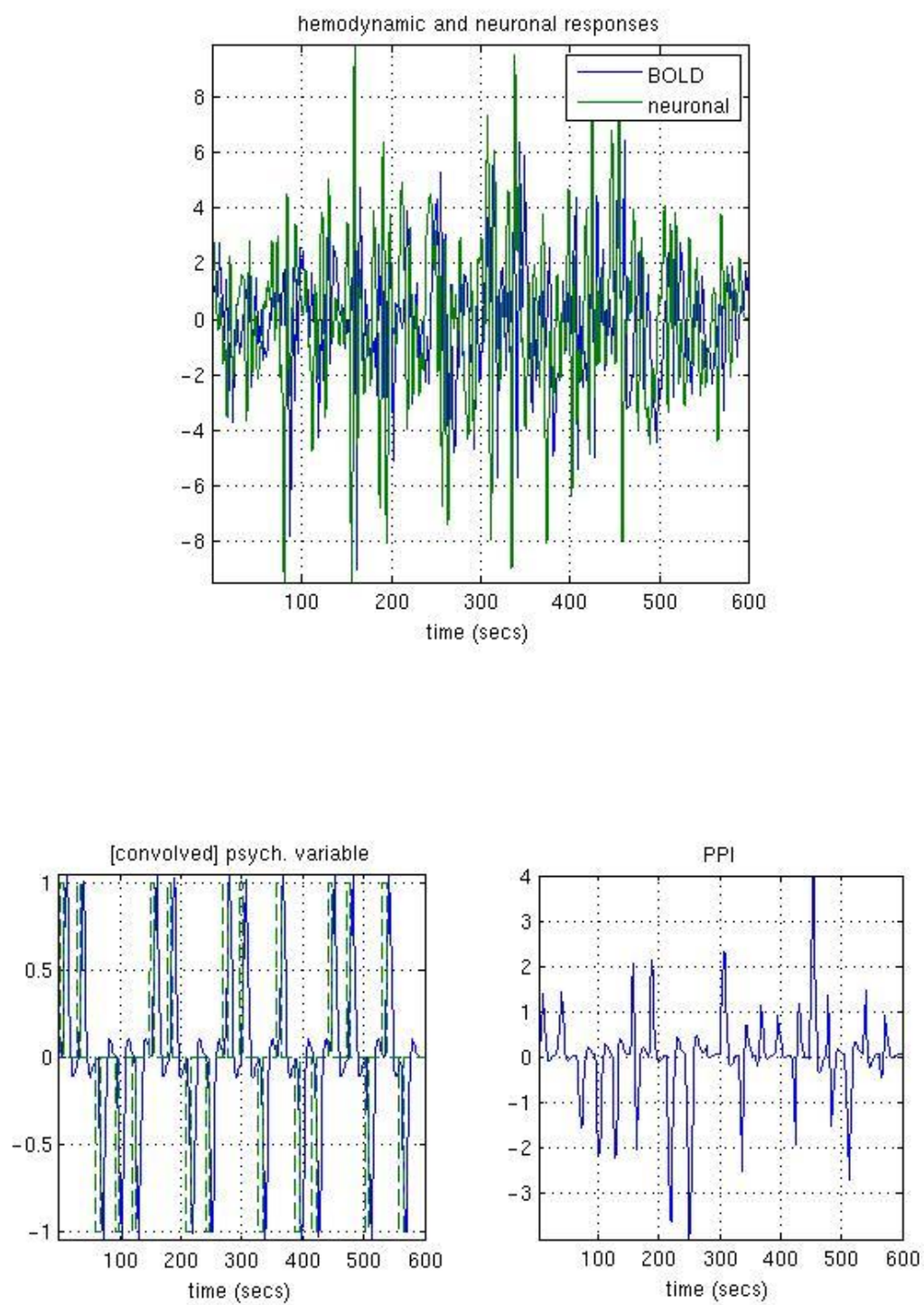
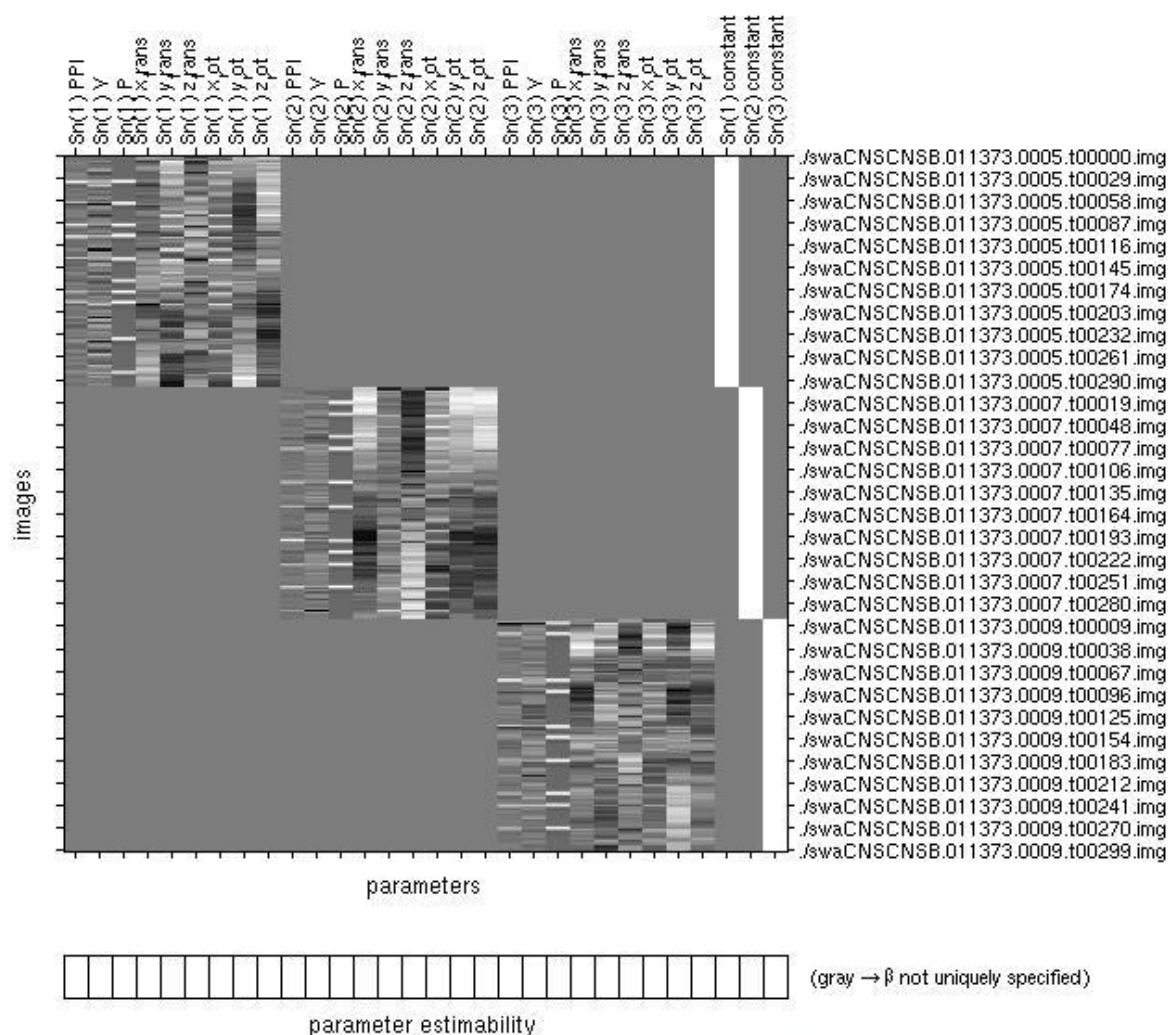


Figure 4-6: Physiological, psychological and PPI regressors

Statistical analysis: Design



Design description...

Basis functions : hrf
Number of sessions : 3
Trials per session : 0 0 0
Interscan interval : 2.00 {s}
High pass Filter : Cutoff: 180 {s}
Global calculation : mean voxel value
Grand mean scaling : session specific
Global normalisation : None

Figure 4-7: Design matrix for PPI analysis

Chapter 5 BEHAVIOURAL RESULTS

5.1 RECRUITMENT

127 potential participants were screened. Of these, 31 had a diagnosis other than AD (MCI or dementia of another type), 24 declined to take part, 18 were deemed unable to undergo an MRI scan at 3T following review of their medical records, 12 were too cognitively impaired, 5 were unsuitable due to behavioural and psychiatric symptoms, 4 were concurrently involved in another research study and 2 were due to move out of area. Therefore 94 potential participants were excluded and 33 participants met inclusion criteria and were recruited. Two of these participants were unable to tolerate the baseline MRI scan and withdrew consent prior to randomisation, and one subject became physically unwell during time between recruitment and baseline assessment. Therefore 30 participants were randomised into 2 equal groups of 15.

All 30 participants completed all training or control sessions and both fMRI scans. The study was well tolerated and there was no drop out post randomisation. Behavioural results are therefore reported on all participants (training group $n = 15$ and control group $n = 15$). A flow chart of recruitment and drop out is shown in Figure 5-1.

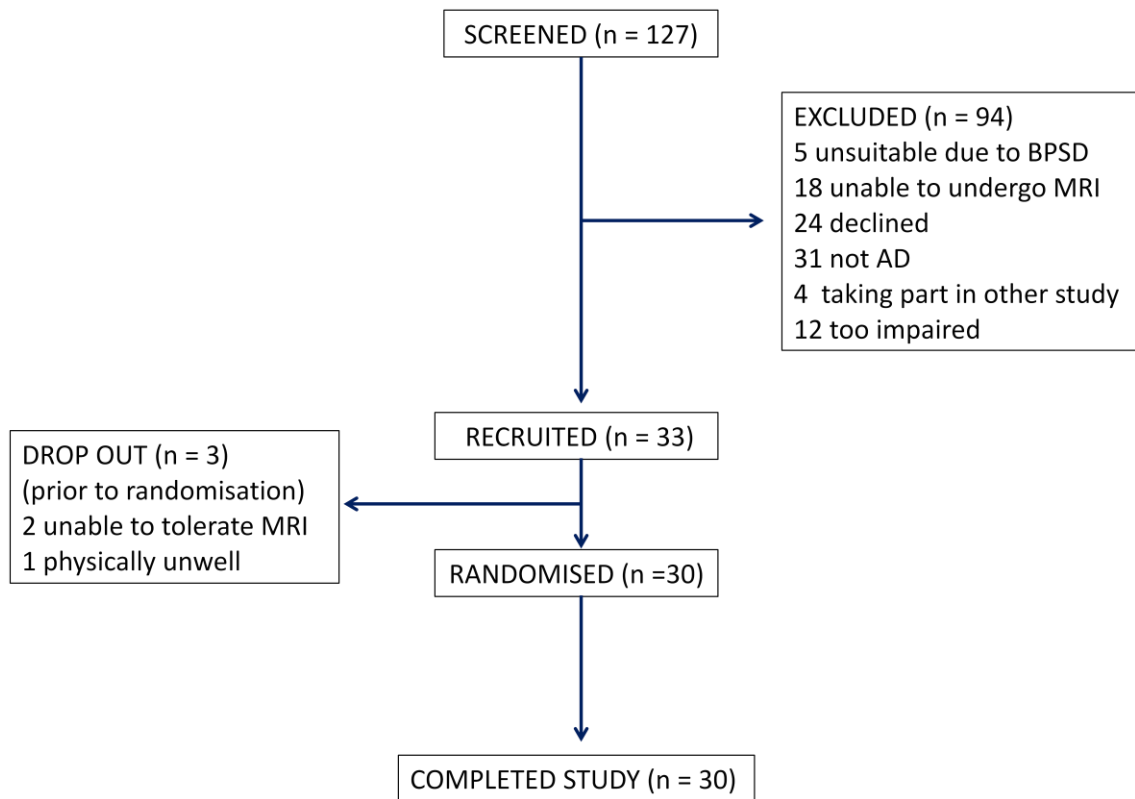


Figure 5-1: Flow chart of recruitment

5.2 DEMOGRAPHIC AND SCREENING ASSESSMENTS

5.2.1 SCREENING TASKS

The results of the screening assessments and demographic variables are shown in Table 5-1. There were no significant differences between the groups in age, gender, years of education, premorbid IQ (as measured using the NART¹⁴⁴), or baseline MMSE⁷¹ score. All participants were right handed. Scores on the screening assessments for mood (GDS¹⁴⁷), neuropsychiatric symptoms (NPI¹⁵⁰), parkinsonian features (Webster¹⁵¹) and cerebrovascular risk factors (Hachinski¹⁴⁹) were all below the respective cut-offs, with no significant differences between the groups. The majority of participants were on stable doses of antimentia medication (cholinesterase inhibitors or memantine). The randomization procedure had therefore produced well matched groups.

	CONTROL (n = 15) Mean (SD)	TRAINING (n = 15) Mean (SD)	RANGE	F value (z value)	Sig (p)
AGE	80.13 (5.19)	79.40 (6.19)	65 - 88	0.124	0.728
MMSE	25.93 (2.09)	26.00 (2.30)	22 - 30	0.007	0.934
YRS ED	12.57 (2.82) [#]	12.33 (2.94)	10 - 20	-0.212*	0.832*
IQ	115.63 (6.78)	117.14 (6.80)	100 - 126	0.370	0.548
GDS	3.73 (2.25)	4.33 (1.99)	0 - 9	-0.784*	0.433*
HACHINSKI	1.79 (1.37) [#]	1.40 (1.24)	0 - 5	-0.515*	0.606*
NPI	3.20 (5.43)	0.93 (2.84)	0 - 18	-1.381*	0.167*
WEBSTER	1.33 (1.40)	0.93 (1.67)	0 - 6	0.507	0.482
GENDER	6 F 9 M	6 F 9 M		0.000	1.000
MEDS	12	11		0.175	0.679

Table 5-1: Demographic and screening variables
MMSE= Mini mental state examination, YRS ED= years of education, GDS = Geriatric Depression scale, NPI= neuropsychiatric inventory, F=female, M=male, MEDS= subject taking prescribed antedementia medication (cholinesterase inhibitors or memantine). [#]n=14. *z values and significance are from Mann-Whitney U and Wilcoxon W Tests, due to non parametric data.

5.3 PRIMARY OUTCOME MEASURES

5.3.1 DIGIT SPAN

5.3.1.1 DIFFERENCE BETWEEN STRUCTURED AND RANDOM TRIALS AT BASELINE

At baseline, participants scored significantly higher on structured compared to random trials. Repeated measures analysis of variance (ANOVA) with trial type as the within participants factor and group as a between participants factor, revealed a significant main effect of trial type ($F(1, 28) = 20.388, p < 0.001$), and no significant interaction between trial type and group ($F(1, 28) = 2.504, p = 0.125$) (Table 5-2, Figure 5-2 and Figure 5-3).

	CONTROL	TRAINING	BOTH
	MEAN (SD)	MEAN (SD)	MEAN (SD)
STR	5.53 (0.90)	5.49 (0.92)	5.51 (0.89)
RAND	5.01 (0.88)	5.23 (0.84)	5.12 (0.85)

Table 5-2: Mean digit span score and standard deviation (SD) at baseline.

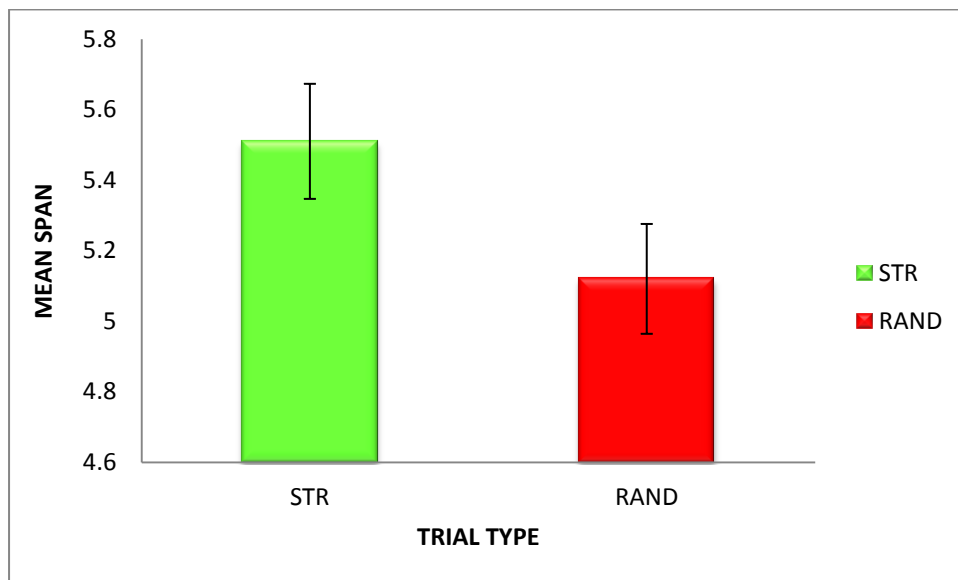


Figure 5-2: Mean digit span score for both groups combined. Error bars are the standard error of the mean (SEM). The main effect of trial type was significant ($p < 0.001$).

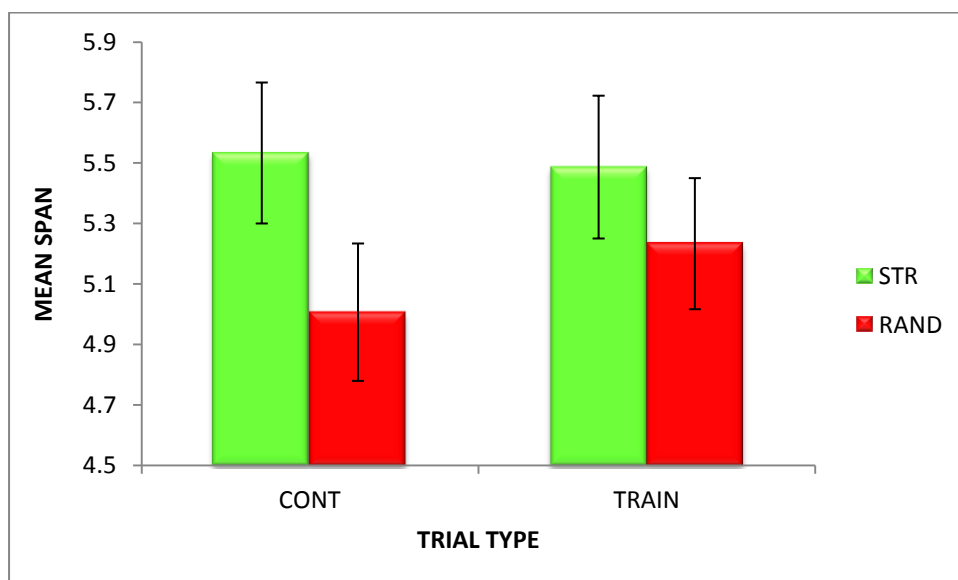


Figure 5-3: Mean digit span score shown by trial type and group. Error bars are SEM.

Table 5-2: Mean digit span score and standard deviation (SD) at baseline. displays mean scores for each group and trial type. T statistics and significance values are shown. Figure 5-2 shows the mean span scores for both groups combined, and Figure 5-3 shows mean span scores separately for each group.

5.3.1.2 DIFFERENCE IN DIGIT SPAN SCORES PRE AND POST INTERVENTION

To examine overall differences in span scores following the control and training interventions, the change in scores for both random and structured trials was calculated (mean score post – mean score pre). Examining both trial types together revealed an increase in span score of mean = 0.29 (Standard deviation (SD) 0.52) in the control group and mean = 0.61 (SD 0.43) in the training group. An independent one tailed T test revealed a significant difference between the groups ($T(28) = -1.82$, $p = 0.040$). (Two-tailed independent T test $p = 0.079$) (Figure 5-4).

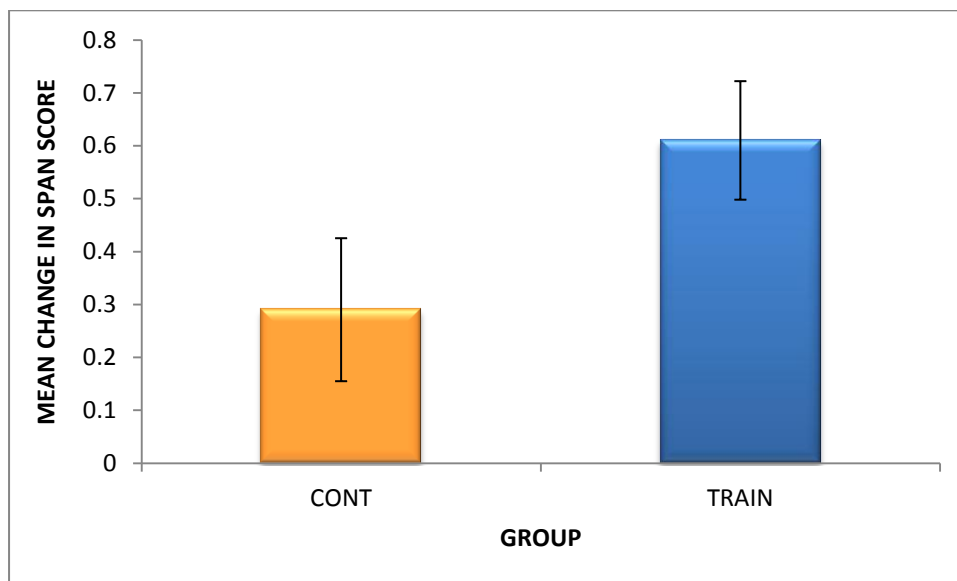


Figure 5-4: Mean change in digit span score averaged across both structured and random trials. Group difference $p = 0.04$ (1- tailed)

In order to further examine whether the change in span scores following the intervention differed according to trial type (structured or random), a repeated measures ANOVA was performed examining mean span scores for structured and random trials at each time point. Time and trial type were within participants factors and group was the between participants factor. This revealed a main effect of time ($p < 0.001$) and a non significant interaction between time and group ($p = 0.079$), however there was a borderline significant complex interaction between time, trial type and group ($p =$

0.053). Therefore separate repeated measures ANOVA were performed for each trial type, with time as the within participants factor and group as the between participants factor.

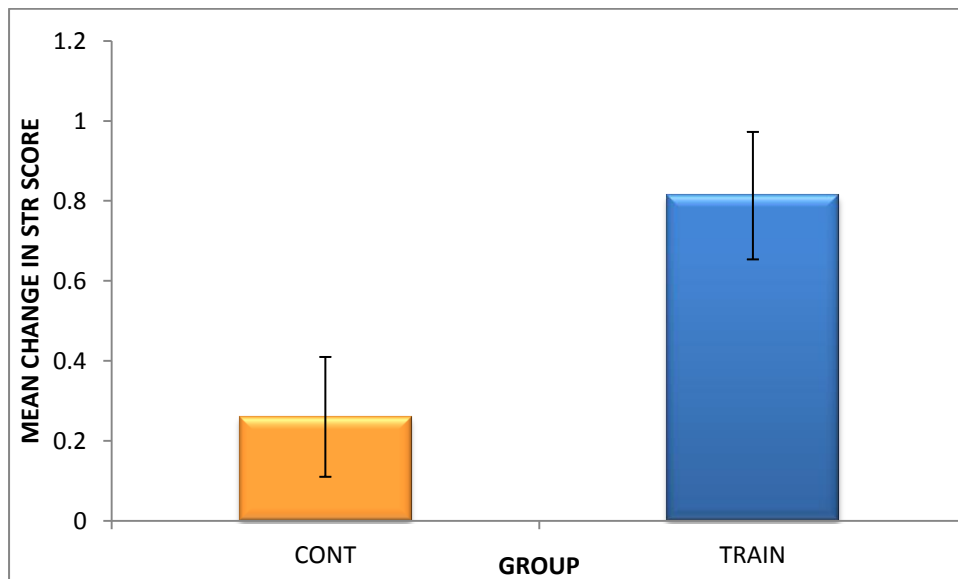


Figure 5-5: Mean change in structured digit span score due to intervention. Error bars are SEM. There is a significant difference between groups ($p=0.017$).

Analysis of the structured trials revealed a significant main effect of time ($F(1, 28) = 24.07, p < 0.001$) and a significant time \times group interaction ($F(1, 28) = 6.40, p = 0.017$). There was no significant between participants effect of group ($F(1, 28) = 0.59, p = 0.447$). The significant interaction is shown as a difference in change score for structured trials in Figure 5-5. Paired T tests were subsequently conducted as post-hoc analyses to investigate the time \times group interaction. The control group demonstrated a non significant increase in span score ($p = 0.115$), however the training group had a highly significant improvement in structured span score following training ($p < 0.001$). The mean span and paired T test results are shown in Table 5-3 and Figure 5-6.

Analysis of random trials revealed a significant main effect of time ($F(1, 28) = 13.025, p = 0.001$) but no significant interaction between time and group ($F(1, 28) = 0.185, p = 0.670$). There was no main effect of group ($F(1, 28) = 0.920, p = 0.346$). Mean scores and paired T test results are shown in Table 5-3 and Figure 5-7.

	PRE MEAN (SD)		POST MEAN (SD)		PRE-POST PAIRED T TEST	
	STR	RAND	STR	RAND	STR	RAND
CONT	5.53 (0.90)	5.01 (0.88)	5.79 (0.75)	5.33 (0.69)	p = 0.105	p = 0.056
TRAIN	5.49 (0.92)	5.23 (0.84)	6.30 (0.90)	5.64 (0.85)	p < 0.001	p = 0.008

Table 5-3 : Mean and (standard deviations) for structured and random digit span trials pre and post intervention. Significance values for paired T tests shown. STR = structured trials, RAND = Random trials.

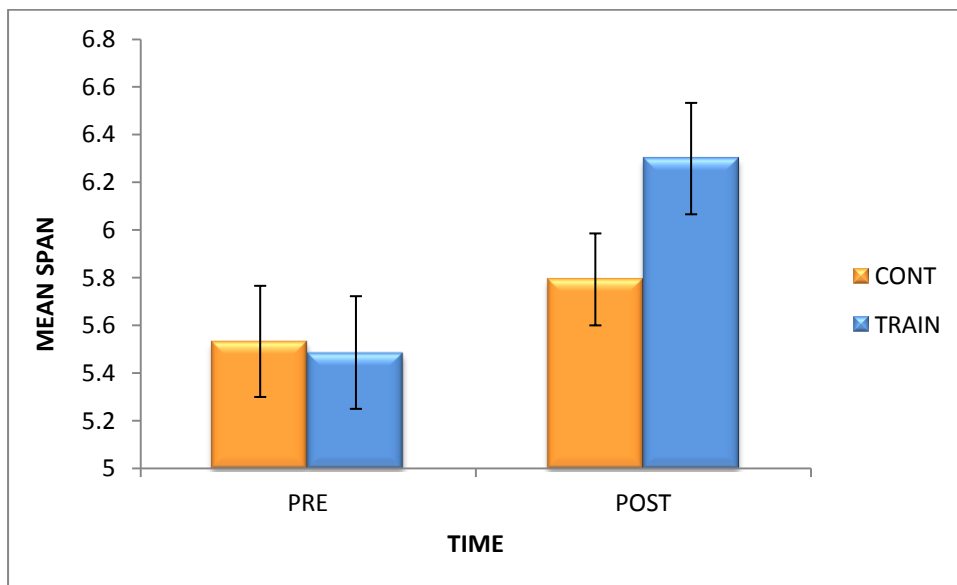


Figure 5-6: Mean digit span score on structured trials at pre and post intervention. Error bars are SEM.

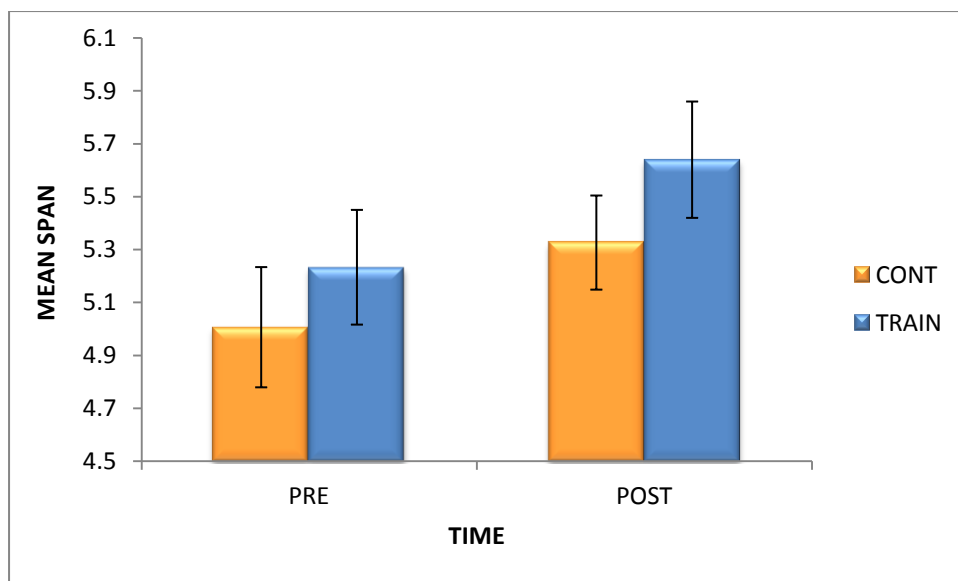


Figure 5-7: Mean digit span scores on random trials at pre and post intervention. Error bars are SEM.

5.3.1.3 EFFECT OF TRAINING ON CHUNKING

A value for chunking was calculated by (mean structured score – mean random score) for each subject. This was calculated at both pre and post time points. A repeated measures ANOVA was then performed. This revealed non significant main effects of time ($F(1, 28) = 2.24, p = 0.145$) and group ($F(1, 28) = 0.103, p = 0.750$) however the interaction between time and group was borderline significant ($F(1, 28) = 4.067, p = 0.053$). As the time x group interaction approached significance, paired tests were conducted to examine the effects within each group separately. The control group had no significant change in chunking ($t(14) = 0.436, p = 0.436$), however the training group significantly improved in their ability to chunk ($t(14) = -2.186, p = 0.046$). Means, SDs and paired T-test results are shown in Table 5-4 and Figure 5-8.

	CONTROL	TRAINING
PRE CHUNKING	0.53 (0.39)	0.25 (0.54)
POST CHUNKING	0.47 (0.49)	0.66 (0.43)
T statistic	0.436	-2.186
p value	0.669	0.046

Table 5-4: Mean (SD) chunking effect (STR-RAND score) pre- and post-intervention and paired T test results.

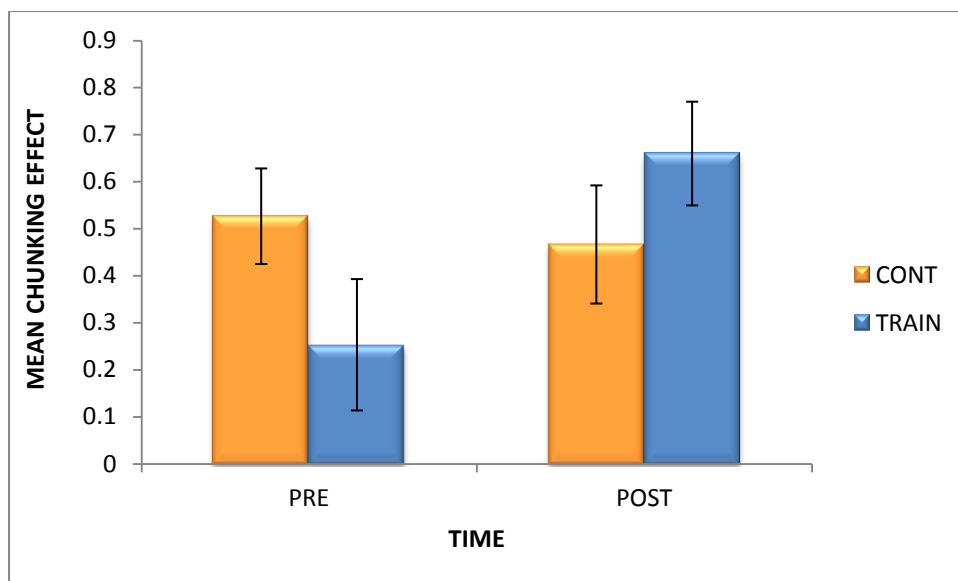


Figure 5-8: Mean chunking scores pre and post intervention on digit span task. Error bars are SEM.

5.3.2 SPATIAL SPAN

5.3.2.1 DIFFERENCE BETWEEN STRUCTURED AND RANDOM TRIALS AT BASELINE

At baseline, all participants scored significantly higher on structured compared to random trials (Table 5-5). Repeated measures analysis of variance (ANOVA), with trial type as the within participants factor and group as the between participants factor, revealed a significant main effect of trial type ($F(1, 28) = 14.628, p = 0.001$), and no significant interaction between trial type and group ($F(1, 28) = 0.870, p = 0.359$). The between participants effect of group was non significant ($F(1, 28) < 0.001, p = 0.991$) (Figure 5-9 and Figure 5-10).

	CONTROL	TRAINING	BOTH
	MEAN (SD)	MEAN (SD)	MEAN (SD)
STR	3.90 (0.70)	3.83 (1.05)	3.86 (0.88)
RAND	3.56 (0.75)	3.62 (0.91)	3.59 (0.82)

Table 5-5: Mean and SD for spatial span scores by trial type at baseline

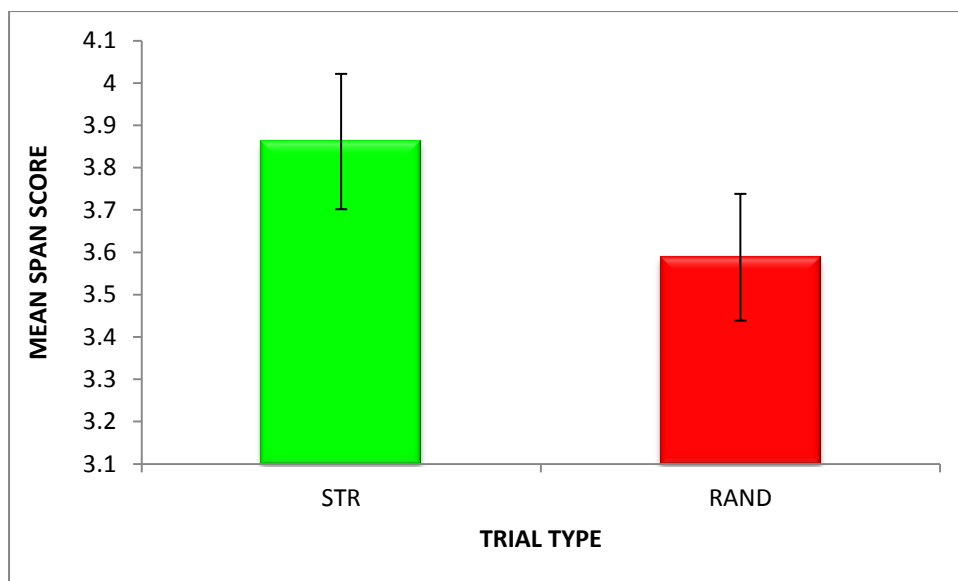


Figure 5-9: Mean spatial span score by trial type
Error bars are SEM.

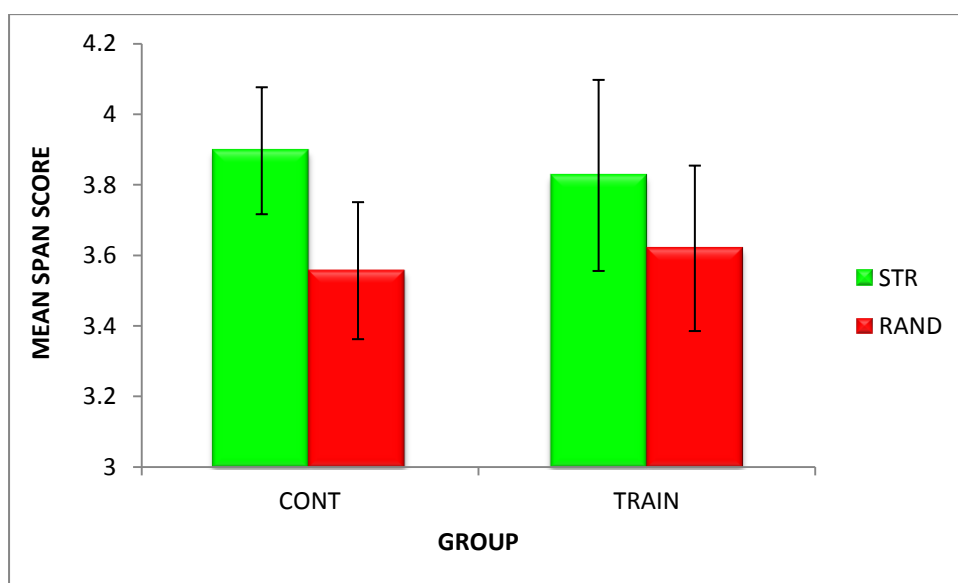


Figure 5-10: Mean spatial span score at baseline by group and trial type
Error bars are SEM.

5.3.2.2 EFFECT OF TRAINING

To examine overall differences in span scores following the control and training interventions, the change in scores for both random and structured trials was calculated (mean score post – mean score pre). Examining both trial types together revealed a mean increase in span score of 0.16 (SD 0.36) in the control group and 0.14 (SD 0.57) in the training group (Figure 5-11). An independent two

tailed T test revealed no significant difference between the groups ($t(28) = 0.144$, $p = 0.886$). Means and SD for group, trial type and time are shown in Table 5-6.

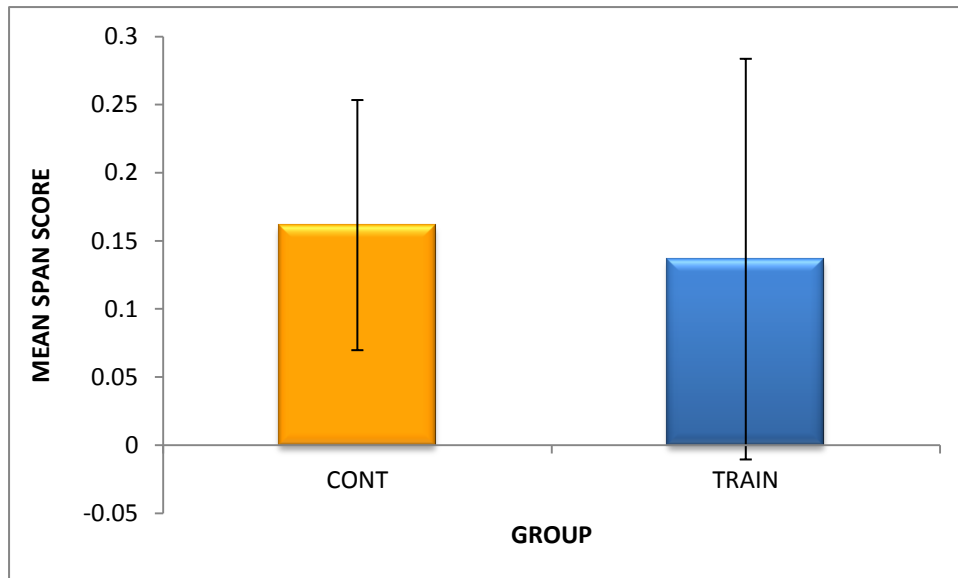


Figure 5-11: Mean change on spatial scan score post – pre
Error bars are SEM.

	PRE		POST		POST- PRE FOR ALL TRIALS
	STR	RAND	STR	RAND	
CONT	3.90 (0.70)	3.56 (0.75)	4.04 (0.82)	3.74 (0.85)	0.16 (0.36)
TRAIN	3.83 (1.05)	3.62 (0.91)	3.98 (0.66)	3.74 (0.59)	0.14 (0.57)

Table 5-6: Means and (SD) for spatial span

Repeated measures ANOVA, with time and trial type as within participants factors and group as the between participants factor demonstrated no significant main effects of time ($F(1, 28) = 2.960$, $p = 0.096$) or group ($F(1, 28) = 0.003$, $p = 0.954$). However the main effect of trial type was significant ($F(1, 28) = 24.044$, $p < 0.001$). There were no significant interactions between time and group ($F(1, 28) = 0.021$, $p = 0.886$), or time x trial type x group ($F(1, 28) = 0.119$, $p = 0.733$).

5.3.2.3 EFFECT OF TRAINING ON CHUNKING

A value for chunking was derived by calculating (mean structured score – mean random score) for each subject. This was calculated at both pre and post time points. A repeated measures ANOVA

was then performed with time as a within participants factor and group as the between participants factor. This revealed no significant main effects of time ($F(1, 28) < 0.001, p = 0.987$), or group ($F(1, 28) = 0.783, p = 0.384$) and as already noted, a non significant interaction between time and group ($F(1, 28) = 0.119, p = 0.733$). The mean chunking scores for each group are shown in Figure 5-12.

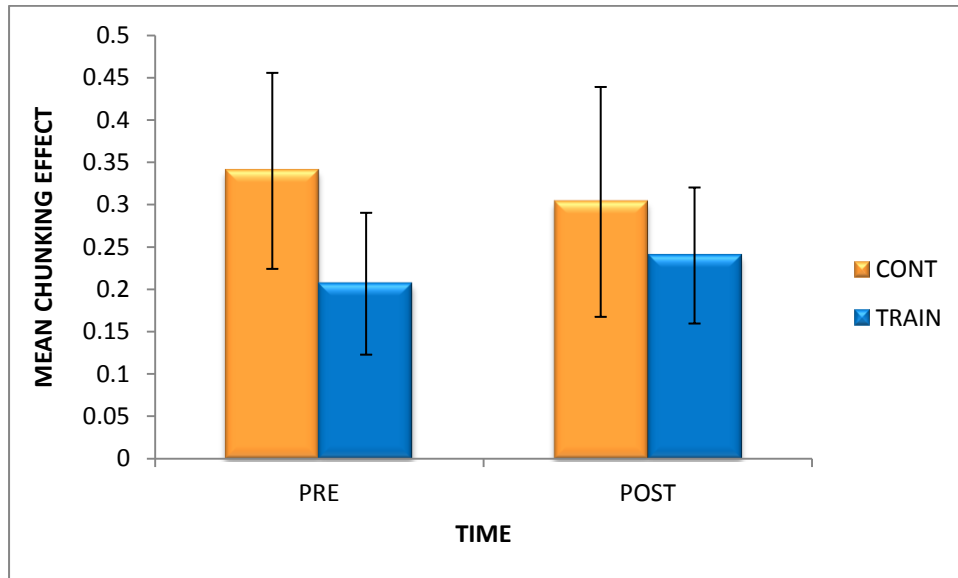


Figure 5-12: Chunking scores for each group at each time point on spatial span task. Error bars are SEM.

5.4 SECONDARY OUTCOME MEASURES

5.4.1 GENERAL COGNITIVE FUNCTION OUTCOME MEASURES

5.4.1.1 MMSE

Repeated measures ANOVA revealed a significant main effect of time ($F(1, 28) = 5.467, p = 0.027$) and a significant interaction between time and group ($F(1, 28) = 7.383, p = 0.011$). The between participants effect of group was non significant ($F(1, 28) = 1.231, p = 0.277$). As there was a significant group x time interaction, paired T tests were performed to examine each group. The control group significantly declined in MMSE score ($T(14) = 3.84, p = 0.002$), whilst the training group demonstrated a non significant increase in score ($T(14) = -0.252, p = 0.805$). Results are shown in Table 5-7 and Figure 5-13.

	CONT Mean (SD)	TRAIN Mean (SD)
MMSE PRE	25.93 (2.09)	26.00 (2.30)
MMSE POST	24.60 (1.84)	26.10 (2.00)
MMSE T TEST	$p = 0.002$	$p = 0.805$

Table 5-7: Mean scores, SD and results of paired T tests for MMSE.

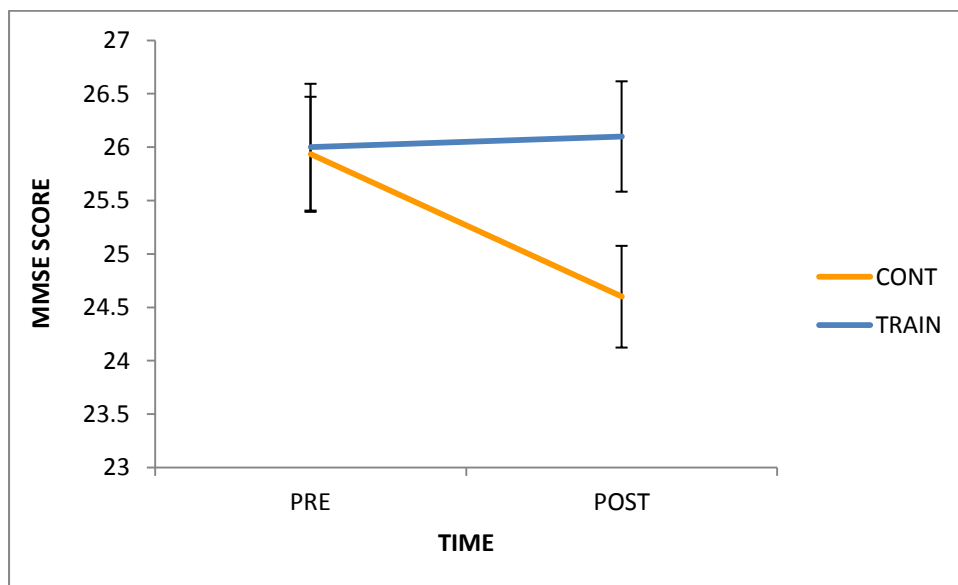


Figure 5-13: Mean MMSE scores pre and post interventions
Error bars are SEM. The time x group interaction is significant ($p = 0.011$).

5.4.1.2 ADAS-Cog⁷²

Results are shown in Table 5-8 and Figure 5-14. As the ADAS-Cog data was not normally distributed, post – pre change in ADAS-Cog scores were calculated and Wilcoxon's rank and Mann-Whitney tests were conducted. Independent samples testing, with post - pre score as the test variable revealed a significant difference between the groups, ($U = 36$, $z = -3.175$, $p = 0.001$ (2-tailed)). As there was a significant group difference, related sample non parametric tests were performed to examine each group. The control group demonstrated a non significant increase in ADAS-Cog score ($z = -1.412$, $p = 0.158$), whilst the training group significantly decreased in score ($Z = -2.670$, $p = 0.008$), representing an improvement in cognitive function following training.

	CONT Mean/Median (SD)	TRAIN Mean/Median (SD)
ADAS-Cog PRE	13.86 / 13.00 (5.72)	14.15 / 11.00 (6.80)
ADAS-Cog POST	14.15 / 14.66 (4.68)	11.55 / 8.67 (6.33)
ADAS-Cog related Wilcoxon ranks test	$p = 0.158$	$p = 0.008$

Table 5-8: Mean, median, SDs and results of related samples non parametric tests for ADAS-Cog

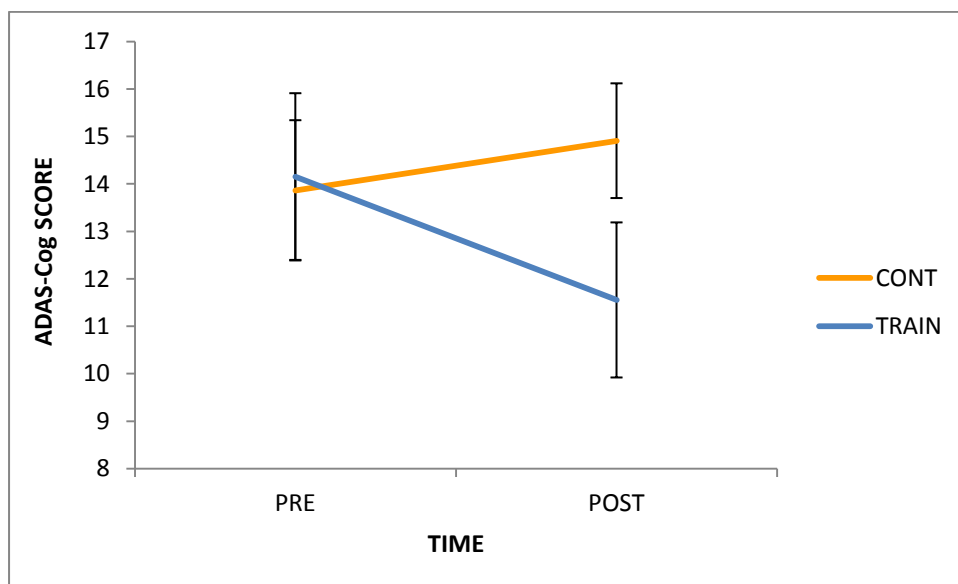


Figure 5-14: Mean ADAS-Cog scores pre and post interventions
Error bars are SEM. The group difference in change scores is significant ($p = 0.001$).

5.4.2 EPISODIC MEMORY OUTCOME MEASURES

Means and SDs for all three tasks assessing episodic memory are shown in Table 5-9.

The paired associate learning (PAL) data was not normally distributed, therefore post – pre change in PAL scores were calculated and Wilcoxon's rank and Mann-Whitney tests were conducted. Repeated measures ANOVAs were conducted for Logical memory data.

	CONT Mean (SD)	TRAIN Mean (SD)
LOG MEM 1 PRE	11.33 (6.00)	10.67 (6.14)
LOG MEM 1 POST	11.87 (4.03)	13.80 (6.87)
LOG MEM 2 PRE	7.93 (7.05)	7.20 (8.20)
LOG MEM 2 POST	7.73 (8.06)	12.47 (8.27)
PAL PRE	3.07 (0.59)	3.47 (0.74)
PAL POST	3.20 (0.94)	3.00 (0.65)

Table 5-9: Means and SDs for episodic memory outcomes

5.4.2.1 LOG MEMORY 1 AND 2¹⁷⁴

Results are shown in Table 5-9, Figure 5-15 and Figure 5-16. A repeated measures ANOVA with time and task (log mem 1 vs log mem 2) as within participants factors and group as the between participants factor was performed. There were significant main effects of time ($F(1, 28) = 8.029, p = 0.008$) and task ($F(1, 28) = 7.848, p = 0.009$). The between participants main effect of group was non significant ($F(1, 28) = 0.402, p = 0.531$). There was a significant interaction between time and group ($F(1, 28) = 6.850, p = 0.014$), but no significant interaction between time x task x group ($F(1, 28) = 1.50, p = 0.231$). Therefore there was a significant improvement in verbal episodic memory function following training compared to controls.

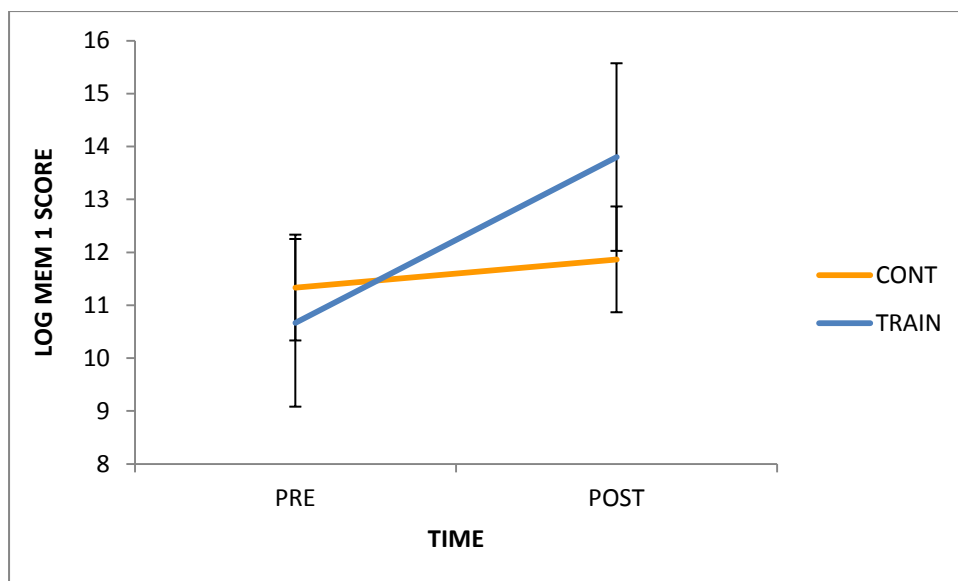


Figure 5-15: Mean Log memory 1 scores. Error bars are SEM

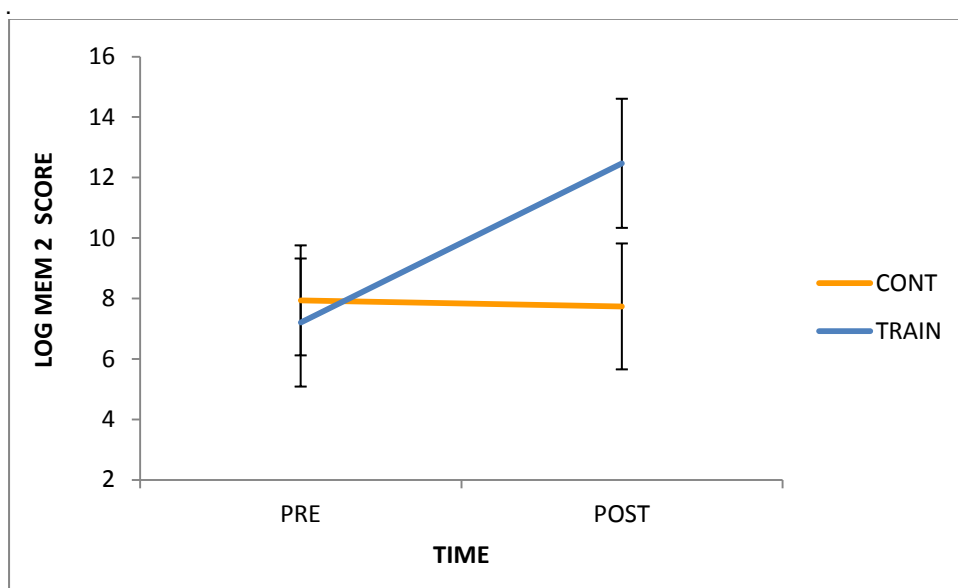


Figure 5-16: Mean Log memory 2 scores
Error bars are SEM. The time x group interaction is significant ($p = 0.014$).

5.4.2.2 PAIRED ASSOCIATES LEARNING¹⁵⁷

Results are shown in Table 5-9 and Figure 5-17. Independent samples testing, with post-pre score as the test variable revealed no significant difference between the groups, ($U = 71.5$, $z = -1.783$, $p = 0.075$ (2-tailed)).

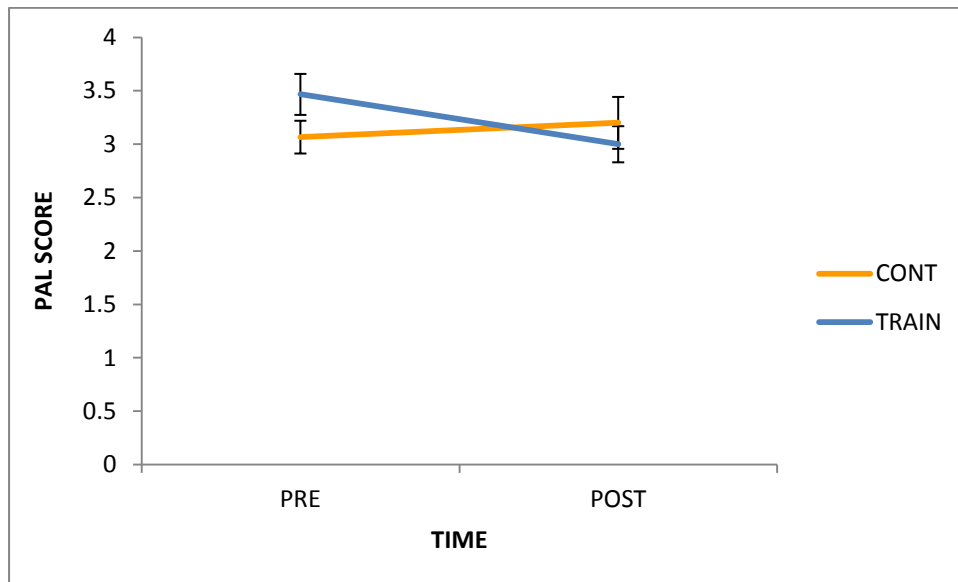


Figure 5-17: Mean Paired Associate Learning (PAL) score
Error bars are SEM. Group difference is non significant ($p = 0.075$).

5.4.3 EXECUTIVE FUNCTION OUTCOME MEASURES

Six tasks were used to assess varying aspects of executive function. These were verbal fluency¹⁷⁵, Trail making test parts A and B¹³⁸, Grammatical reasoning (GR)¹⁵⁷, odd one out (OOO)¹⁵⁷ and self ordered search (SOS)¹⁵⁷.

The Trail making test part B was not included in the analysis as 7 out of 14 control participants and 11 out of 15 training participants at baseline, and 50% of each group at follow up failed to complete the task. Therefore significant floor effects were seen with this task, preventing reliable analysis of results.

Data from the Trail making test part A and Self Ordered Search (SOS) tasks were not normally distributed, therefore post – pre change in Trails A and SOS scores were calculated and individual Wilcoxon's rank and Mann-Whitney tests were conducted for these tasks.

Individual repeated measures ANOVAs, with time as the within participants variable and group as the between participants variable were conducted on the fluency, GR and OOO tasks. The repeated measures ANOVAs revealed that there were no significant main effects of time or group and no significant time x group interactions on any of the executive function tasks. Similarly, non parametric independent samples testing, with post-pre score as the test variable revealed no significant differences between the groups on either the Trails A or SOS tasks (see Table 5-10). Figure 5-18, Figure 5-19, Figure 5-20, Figure 5-21 and Figure 5-22 show mean scores on each executive function task included in the analysis.

	CONT	TRAIN	TIME X GROUP F (p)
FLUENCY PRE	8.21 (2.52) ¹	8.64 (2.73)	0.32 (0.577)
FLUENCY POST	8.27 (2.43)	8.00 (2.59)	
GRAM REASON PRE	4.73 (4.59)	6.00 (5.28)	3.44 (0.074)
GRAM REASON POST	6.80 (5.72)	5.40 (4.40)	
ODD ONE OUT PRE	7.60 (2.29)	10.20 (3.10)	2.07 (0.162)
ODD ONE OUT POST	8.53 (3.02)	9.40 (3.42)	
	CONT	TRAIN	MANN WHITNEY U (p)
TRAILS A PRE	77.70 (39.43) ¹	91.34 (81.62)	91.5 (0.556)
TRAILS A POST	78.36 (47.18)	84.63 (59.47)	
SELF ORD SEARCH PRE	4.00 (0.93)	4.87 (1.06)	76.5 (0.121)
SELF ORD SEARCH POST	4.67 (1.05)	4.93 (1.39)	

Table 5-10: Means, SDs and results of individual repeated measures ANOVAs
Results of group x time interactions, and non parametric independent samples tests are shown. ¹n=14, as one control subject had no data for fluency and trails A at baseline.

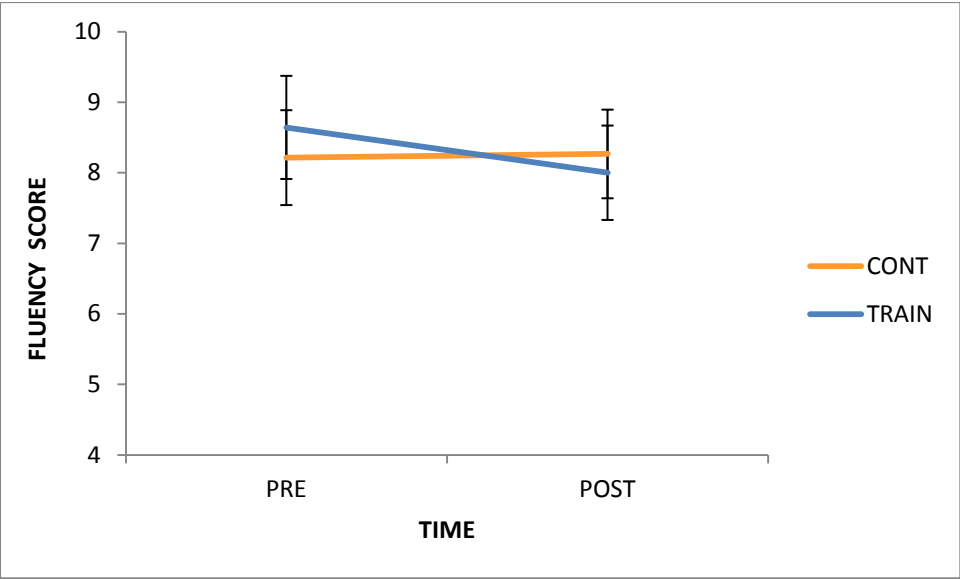


Figure 5-18: Mean verbal fluency scores. Error bars are SEM

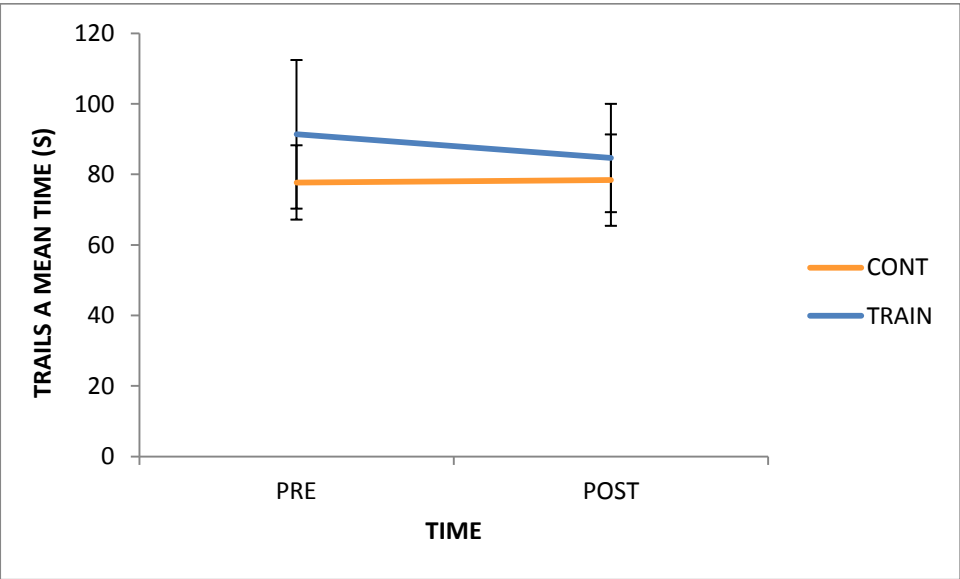


Figure 5-19: Mean times for Trails A task. Error bars are SEM.

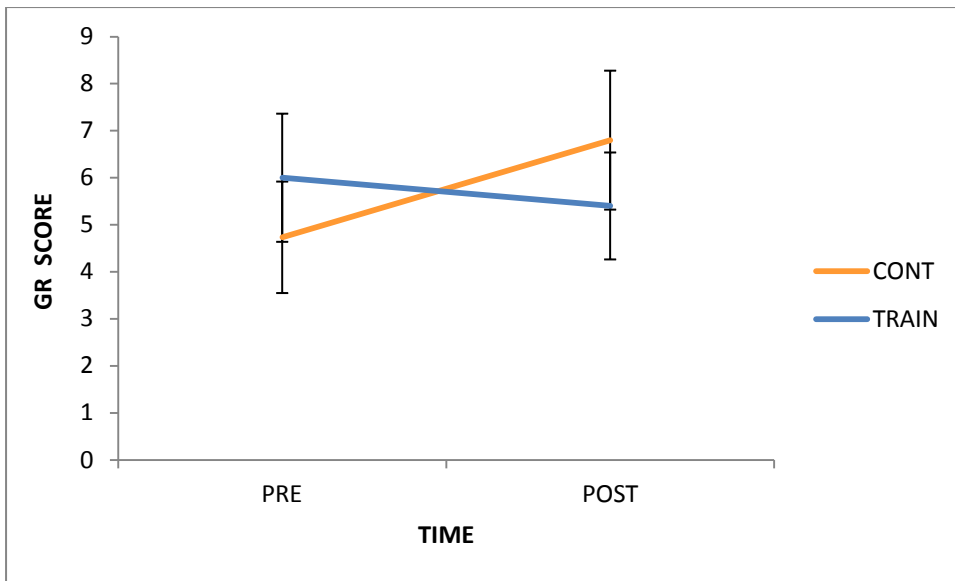


Figure 5-20: Mean score on grammatical reasoning task. Error bars are SEM.

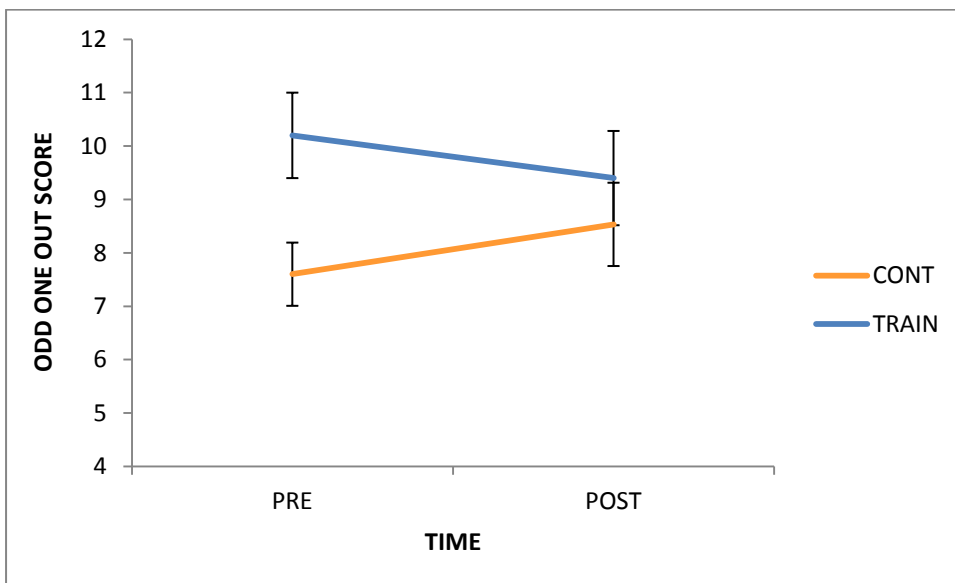


Figure 5-21: Mean score on Odd One Out task. Error bars are SEM.

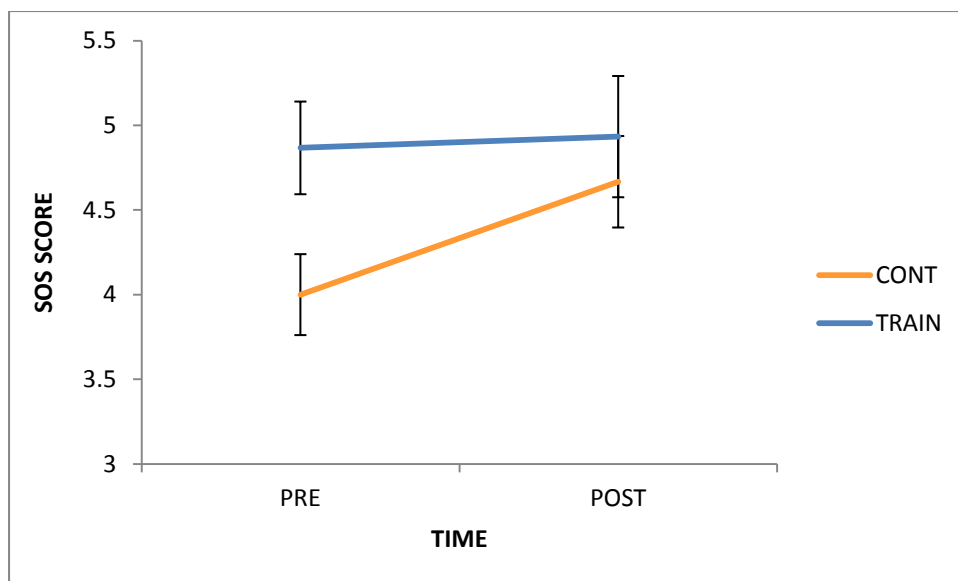


Figure 5-22: Mean score on self ordered search task. Error bars are SEM.

5.4.3.1 SUSTAINED ATTENTION

Sustained attention was measured using the SART¹⁶². The errors were categorised as either omission errors (not responding to the appropriate number) and commission errors (responding to a number 3). An overall error score was calculated by adding the omission and commission errors.

A repeated measures ANOVA, examining overall errors, with time as the within participants factor and group as the between participants factor found no significant main effects of time ($F(1, 23) = 0.239$, $p = 0.630$) or group ($F(1, 23) = 0.093$, $p = 0.763$), and no significant time x group interaction ($F(1, 23) = 2.273$, $p = 0.145$). Individual repeated measures ANOVA for omission errors and commission errors also revealed no significant main effects or interactions (Table 5-11 and Figure 5-23).

	CONT (n=12) ¹	TRAIN (n=13) ¹	Time x group p
SART ERROR PRE	29.17 (25.92)	26.62 (31.63)	0.145
SART ERROR POST	21.33 (17.39)	30.62 (37.17)	
OMISSION PRE	22.42 (22.35)	18.46 (27.74)	0.127
OMISSION POST	15.58 (13.34)	23.62 (33.30)	
COMMISSION PRE	6.75 (4.62)	8.15 (8.42)	0.939
COMMISSION POST	5.75 (4.92)	7.00 (6.67)	

Table 5-11: Mean and SD for error types in SART task

Significance values for time x group interactions from repeated measures ANOVA are also shown. ¹Data only available for 12 controls and 13 training participants at both pre and post.

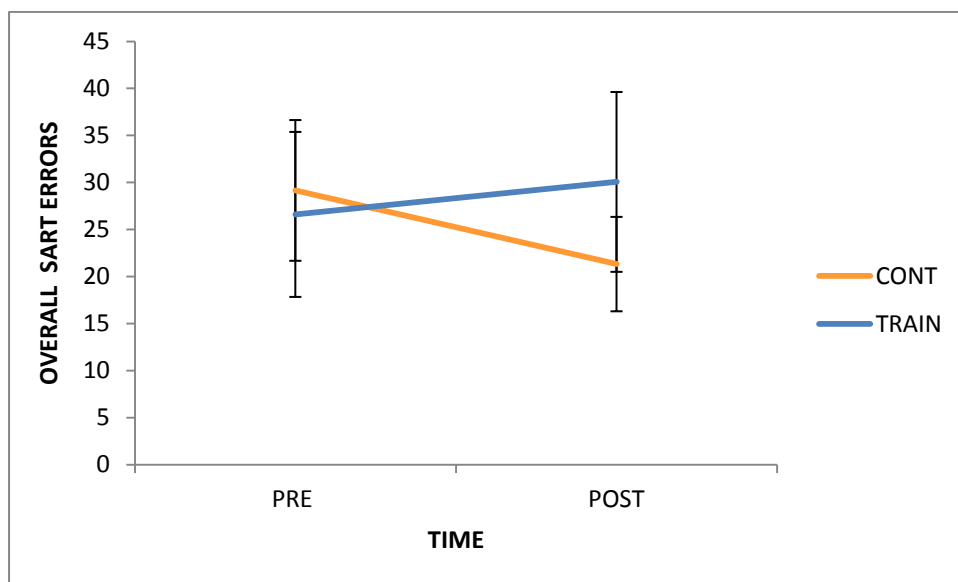


Figure 5-23: Mean overall SART errors. Error bars are SEM.

5.4.4 NON COGNITIVE OUTCOME MEASURES

Results for the IADL¹⁶³ and DEMQOL¹⁶⁴ outcome measures are shown in Table 5-12, Figure 5-24 and Figure 5-25.

	CONT	TRAIN	Time x group (p)
IADL PRE	11.79 (2.01) ¹	12.40 (1.64)	0.620
IADL POST	11.71 (1.98) ¹	12.53 (1.64)	
DEMQOL PRE	98.07 (10.37) ¹	102.13 (6.81)	0.585
DEMQOL POST	98.73 (8.58) ¹	102.60 (5.60)	

Table 5-12: Means, SDs and time x group significance levels for IADL and DEMQOL outcomes
¹n=14

5.4.4.1 INSTRUMENTAL ACTIVITIES OF DAILY LIVING

Repeated measures ANOVA revealed no significant main effects of time ($F(1, 27) = 0.023$, $p = 0.881$) or group ($F(1, 27) = 1.238$, $p = 0.276$) and no significant time x group interaction ($F(1, 27) = 0.251$, $p = 0.620$).

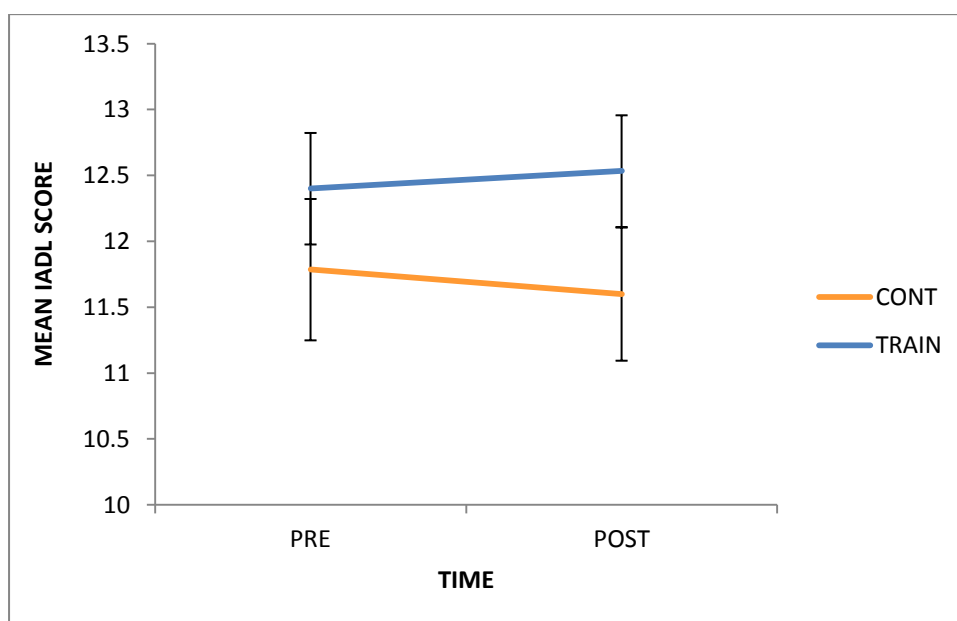


Figure 5-24: Mean IADL scores. Error bars are SEM.

5.4.4.2 DEMQOL

Repeated measures ANOVA revealed no significant main effect of time ($F(1, 27) = 0.890, p = 0.354$) or group ($F(1, 27) = 1.680, p = 0.206$) and no time x group interaction ($F(1, 27) = 0.305, p = 0.585$).

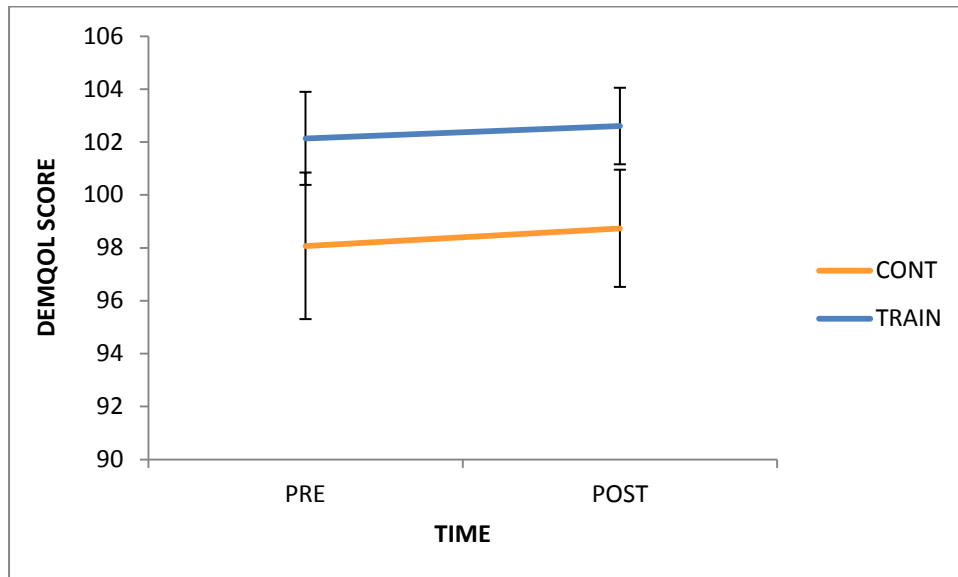


Figure 5-25: Mean DEMQOL score. Error bars are SEM.

5.4.5 METACOGNITION

5.4.5.1 META-MEMORY IN ADULTHOOD QUESTIONNAIRE (MIA)

A repeated measures ANOVA of all sub-category scores and overall score revealed no significant main effects of time ($F(1, 22) = 0.371, p = 0.549$) or group ($F(1, 22) = 0.008, p = 0.928$). There was a non significant interaction between time and group ($F(1, 22) = 1.153, p = 0.295$), however there was a significant time x category x group interaction ($F(1, 22) = 2.575, p = 0.048$). Therefore separate repeated measures ANOVAs were conducted for each category. The results are shown in Table 5-13. For strategy there was a borderline significant main effect of time ($F(1, 22) = 4.071, p = 0.056$) and a significant time x group interaction ($F(1, 22) = 7.854, p = 0.010$), (Figure 5-27). For task, there was a significant main effect of time ($F(1, 22) = 4.866, p = 0.038$), however the time x group interaction was non significant ($F(1, 22) = 3.401, p = 0.079$) (Figure 5-28). All other domains revealed no significant main effects or interactions. (Table 5-13 and Figure 5-26, Figure 5-27, Figure 5-28).

CATEGORY	CONTROL n=10		TRAIN n=14		Time x group p
	PRE	POST	PRE	POST	
STRATEGY	63.00 (9.65)	59.57 (7.96)	57.36 (6.26)	63.00 (8.16)	0.010
TASK	54.91 (4.97)	58.71 (3.83)	56.43 (6.24)	57.07 (3.95)	0.079
CAPACITY	46.91 (7.11)	48.79 (7.89)	48.43 (8.72)	48.00 (8.90)	0.149
CHANGE	38.82 (6.10)	37.71 (9.82)	39.64 (8.67)	41.53 (9.66)	0.116
ANXIETY	47.64 (7.19)	47.21 (9.23)	47.29 (8.48)	44.4 (8.97)	0.289
ACHIEVEMENT	59.73 (7.58)	56.00 (4.79)	58.50 (7.12)	58.67 (6.75)	0.090
LOCUS	29.45 (3.64)	28.50 (4.01)	29.36 (3.73)	29.07 (3.39)	0.628
TOTAL	340.45 (11.07)	336.50 (20.70)	337.00 (0.10)	341.73(20.66)	0.295

Table 5-13: Means, (SDs) and time x group interaction significance values for each of the categories of the MIA.

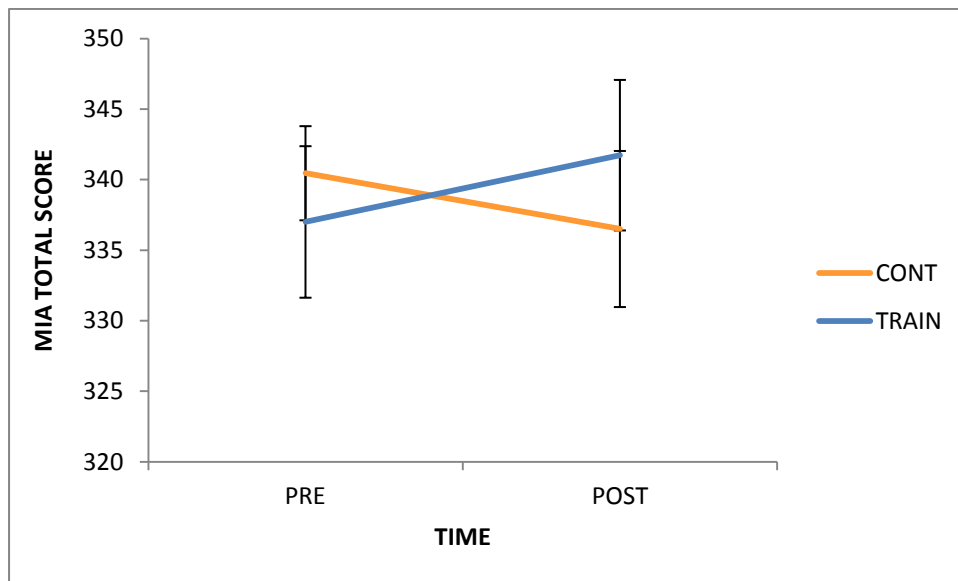


Figure 5-26: Overall mean MIA score. Error bars are SEM.

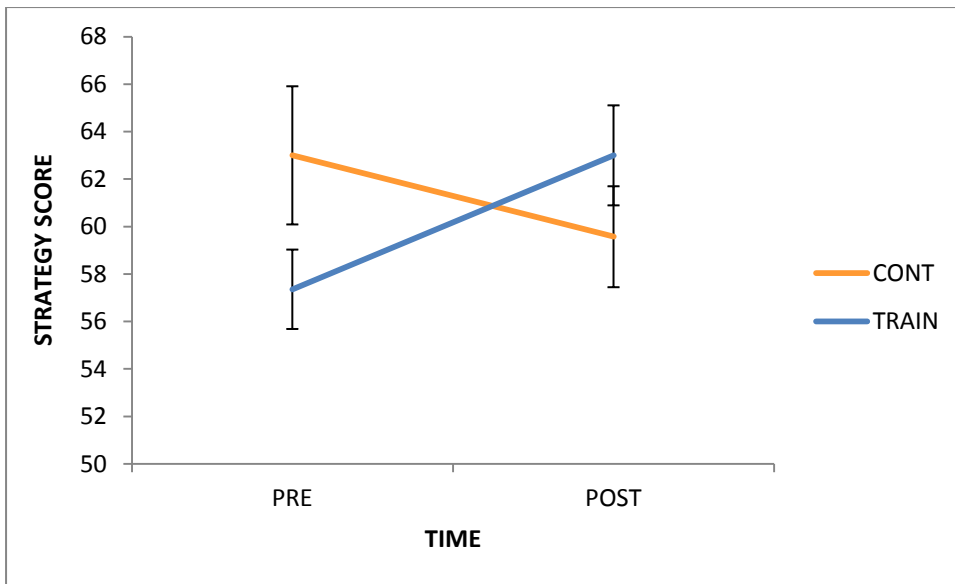


Figure 5-27: Mean strategy score on the MIA
Errors are SEM. The group x time interaction is significant ($p = 0.010$).

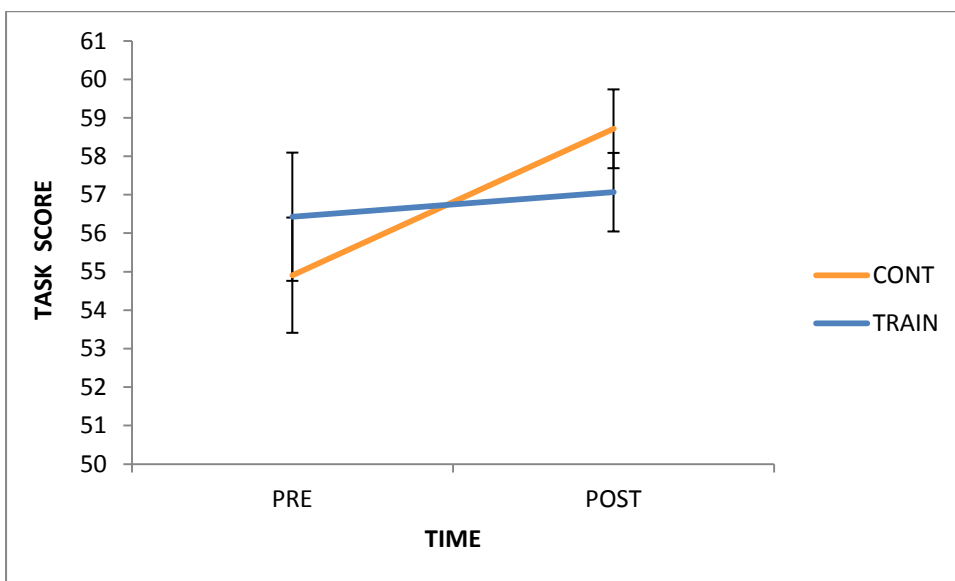


Figure 5-28: Mean task score on the MIA. Error bars are SEM.

5.4.5.2 CHUNKING SUBJECTIVE REPORTS DURING DIGIT SPAN

5.4.5.2.1 Question 1: Did you use any strategy to help you remember?

As can be seen in Table 5-14 and Figure 5-30 , the majority of participants did not report explicitly using chunking strategies at either time point. The percentage of participants using chunking in the training group increased following training, however there were no significant between group differences at either time point, and no paired differences between pre and post responses for either group.

	% CHUNKING		% NOT CHUNKING	
	PRE	POST	PRE	POST
CONT	33.33	26.67	40	53.33
TRAIN	33.33	40	53.33	46.67

Table 5-14: Percentage of participants who explicitly used chunking strategies during digit span tasks
Of note the percentages do not add up to 100%, as table does not show percentages for participants whom it was unclear if chunking strategy used.

5.4.5.2.2 Question 2: Did you find one of the blocks easier?

As shown in Table 5-15 and Figure 5-29, the majority of participants reported noticing no difference between structured and random trial types at either time point. However the percentage in the training group reporting that structured trials were easier doubled from pre (20%) to post (40%), whilst the percentage of control participants reporting that structured trials were easier reduced from 20% (pre) to 6.67% (post). There were no significant group differences at baseline, however at post intervention the group difference on the 'easier' report approached significance ($p = 0.066$). Wilcoxon signed ranks test for paired (pre and post) within group differences was also non significant (Table 5-17, Table 5-18)

	PRE			POST		
	STR EASIER	RAND EASIER	NO DIFF	STR EASIER	RAND EASIER	NO DIFF
CONT	20	6.67	40	6.67	20	46.67
TRAIN	20	0	66.67	40	6.67	46.67

Table 5-15: Percentages of participants by report of which block of trials they found easier to perform
STR easier= structured trials easier, RAND easier = random trials easier, NO DIFF= found no difference between structured and random blocks.

Matching actual performance with perceived easier trial type revealed that at both time points the majority of participants did not correctly match the preferred trial type block with performance at either time point (Table 5-16), however there were no significant group differences or within participants effect of time (Table 5-17, Table 5-18, and Figure 5-31).

	CONT		TRAIN	
	PRE	POST	PRE	POST
MATCH	13.33	20	20	40
NO MATCH	53.33	53.33	66.67	53.33

Table 5-16: Percentages of match between which trial type participants reported as easier and actual performance
Of note the percentages do not add up to 100%, as table does not include participants who had no data.

DS		MANN-WHITNEY U	Z	ASYMP. SIG. (2-TAILED)
PRE	EASIER	99.500	-0.592	0.554
	CHUNK	92.500	-0.898	0.369
	MATCH	105.000	-0.482	0.630

POST	EASIER	71.000	-1.835	0.066
	CHUNK	110.000	-0.114	0.910
	MATCH	90.000	-1.175	0.240

Table 5-17: Mann-Whitney U results for group differences on digit span subjective report measures.

		CHUNK	EASIER	MATCH
CONTROL	Z	-0.750	<0.001	-1.000
	Asymp. Sig. (2-tailed)	0.453	1.000	0.317
TRAIN	Z	-1.510	-0.577	-1.342
	Asymp. Sig. (2-tailed)	0.131	0.564	0.180

Table 5-18: Wilcoxon signed ranks test for paired (pre and post) within group differences on digit span subjective report measures

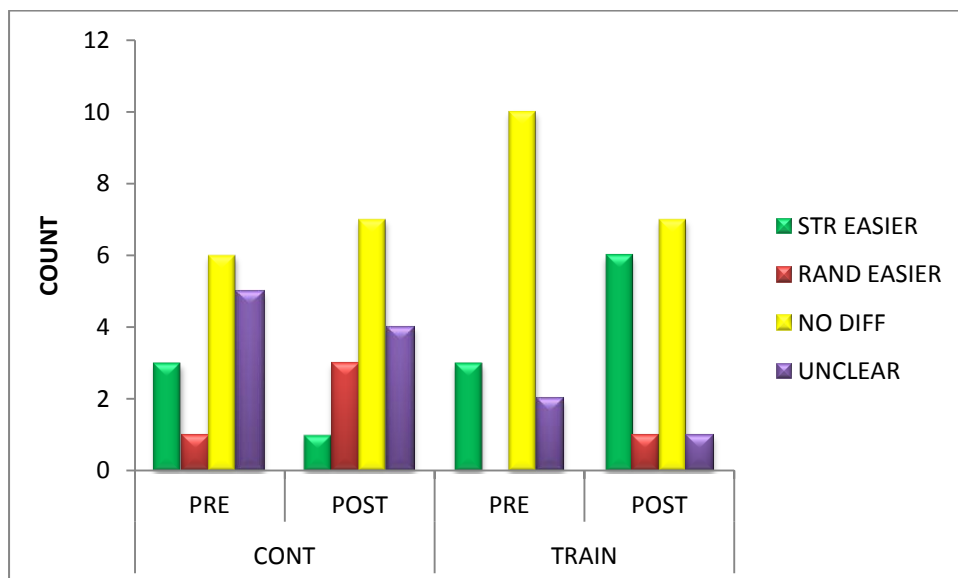


Figure 5-29: Count of participants' reports of which trial type of digit span they found easier to perform.

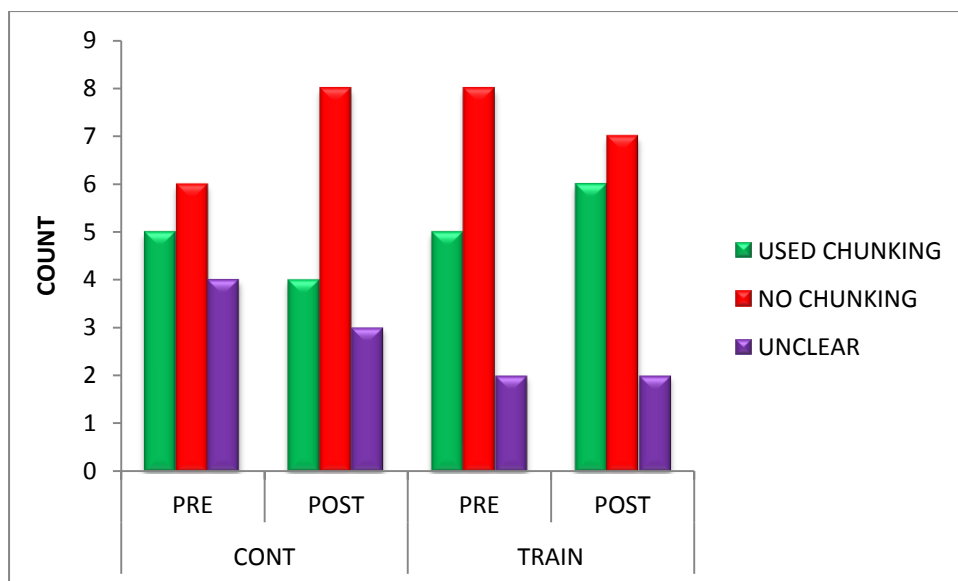


Figure 5-30: Count of participants reporting they explicitly used chunking strategies whilst performing digit span task.

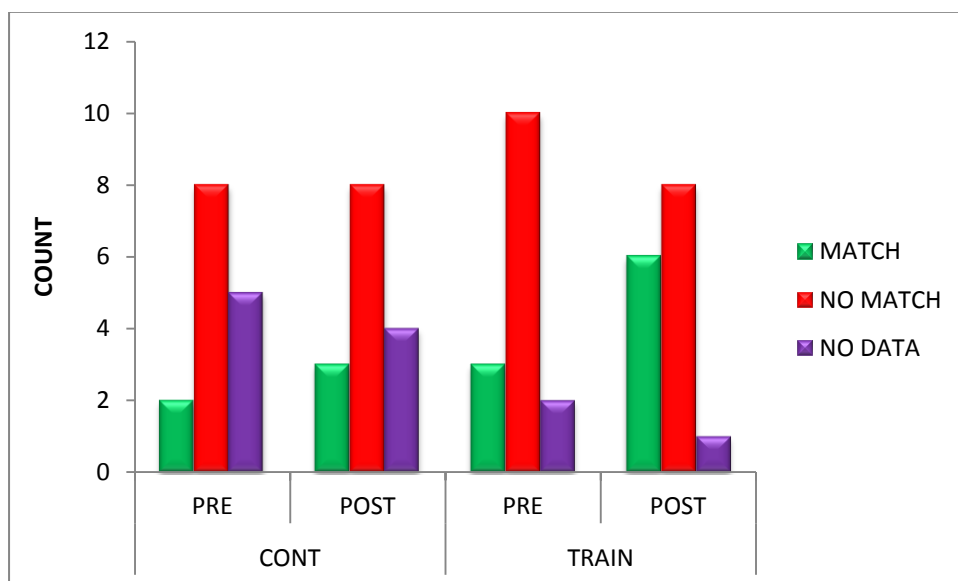


Figure 5-31: Count of numbers of matches between participants' report of which trial type they thought was easier and on which trial type they actually performed better.

Chapter 6 NEUROIMAGING RESULTS

6.1 BEHAVIOURAL RESULTS DURING FMRI

6.1.1 SUMMARY OF PERFORMANCE

As shown in Table 6-1, there were a total of 1714 completed digit span trials in the pre training fMRI session, and 1715 completed trials in the post training fMRI session.

		STRUCTURED	RANDOM
PRE	CONTROL (n= 874)	70.2%	65.1%
	TRAIN (n= 840)	73.9%	72.0%
	TOTAL (n=1714)	72.1%	68.6%
POST	CONTROL (n= 844)	74.1%	71.3%
	TRAIN (n= 871)	78.6%	71.9%
	TOTAL (n= 1715)	76.3%	71.6%

Table 6-1: Percentages of correct trials during fMRI

In the pre training fMRI session, control participants performed better on structured (70.2% correct) than random trials (65.1% correct), and trained participants also performed better on structured (73.9% correct) than random trials (72% correct).

At follow up, control participants performed better on structured trials (74.1%) than random trials (71.3% correct). Trained participants also performed better on structured (78.6% correct) than random trials (71.9% correct).

A repeated measures ANOVA was performed with time point (pre vs. post), trial type (structured vs. random) and correct performance (correct vs. incorrect) as within participants factors, and group as a between participants factor. All significant effects are shown in Table 6-2,

Figure 6-1 and Figure 6-2. There were no other significant main effects or interactions.

SIGNIFICANT RESULTS	F	Sig.
CORRECT (CORRECT vs. INCORRECT)	34.961	<0.001
TRIAL TYPE x CORRECT	6.871	0.014

Table 6-2: Results of repeated measures ANOVA of span performance during fMRI

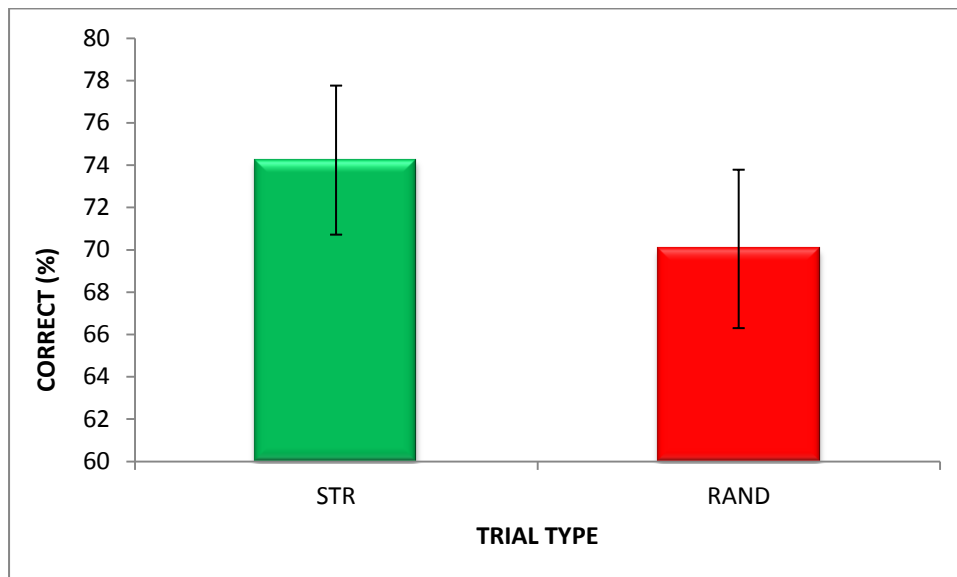


Figure 6-1: Correct trials across both groups and time point
Error bars are SEM. The difference between trial types is significant ($p = 0.014$)

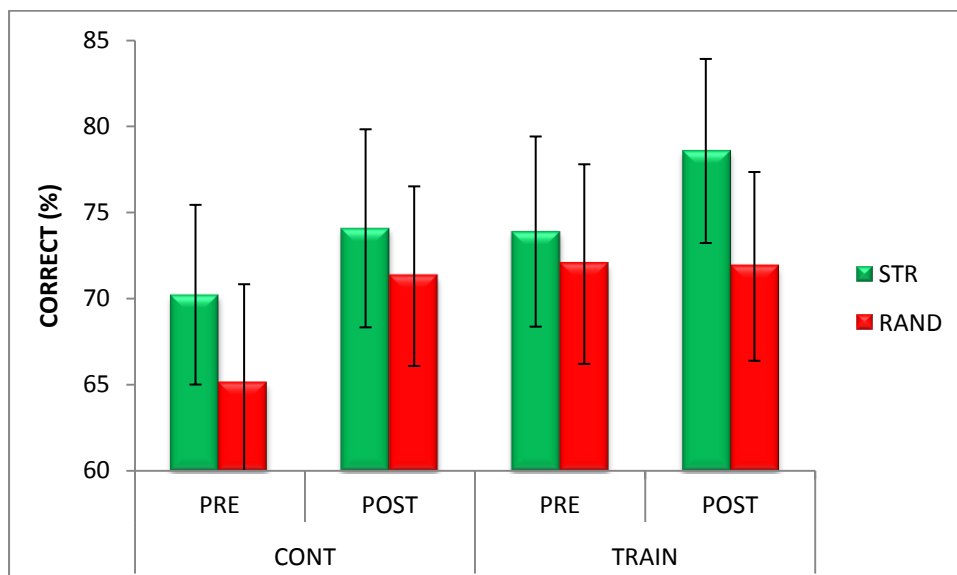


Figure 6-2: Correct trials shown by trial type, group and time. Error bars are SEM.

6.1.2 CONFIDENCE REPORTS DURING FMRI

During fMRI sessions, participants reported on a trial by trial basis whether they were confident that they had correctly recalled the span. These confidence reports were analysed on a trial by trial basis, with a 'match' scored for correct trials with a confident response, or incorrect trials with a not confident report. A 'miss' was scored for correct trials with a not confident report, or incorrect trials with a confident report. Each participant's match and miss scores were calculated for each trial type at each fMRI session.

		CONT (%)		TRAIN (%)	
		PRE	POST	PRE	POST
MATCH	STR	83.4	83.0	81.3	85.8
	RAND	78.1	81.5	80.1	78.3
	TOTAL	80.7	82.3	80.7	82.0

Table 6-3: Percentage of correct matches by trial type and time point
Match = correct trial with confident response or incorrect trial with not confident response.

Table 6-3 and Figure 6-3 show the percentages of matches for each trial type at each time point. A repeated measures ANOVA revealed no main effects of time ($F(1, 27) = 0.479$, $p = 0.495$) or group ($F(1, 27) = 0.001$, $p = 0.976$), however the main effect of trial type was significant ($F(1, 27) = 7.893$, $p = 0.009$). There was a non significant time x group interaction ($F(1, 27) = 0.002$, $p = 0.963$), however the time x trial type x group interaction was significant ($F(1, 27) = 5.326$, $p = 0.029$). Individual repeated measures ANOVA of each trial type revealed no significant main effects or interactions.

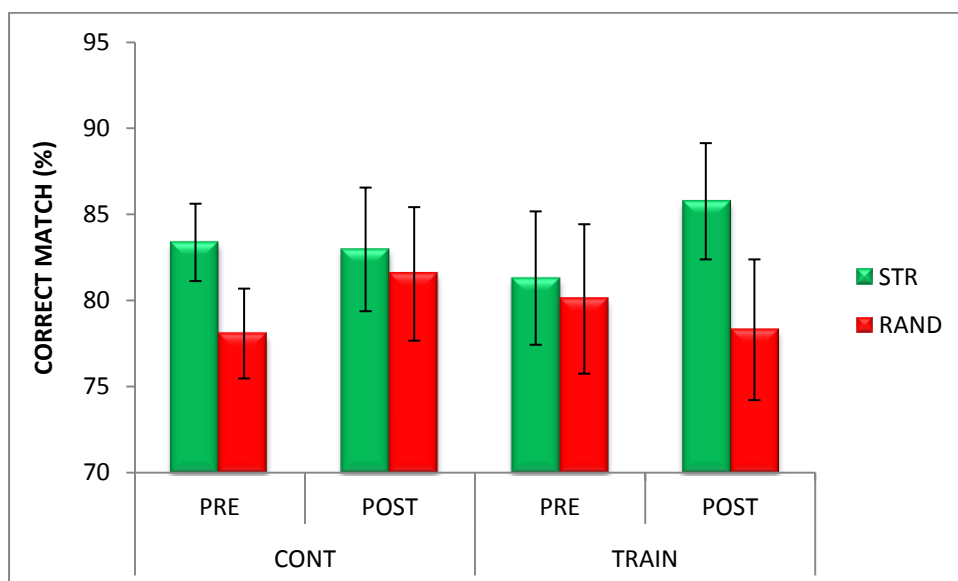


Figure 6-3: Percentage of correct matches by trial type and time point
Error bars are SEM. The time x trial x group interaction was significant ($p = 0.029$).

6.2 FIRST LEVEL – INDIVIDUAL PARTICIPANT ANALYSIS

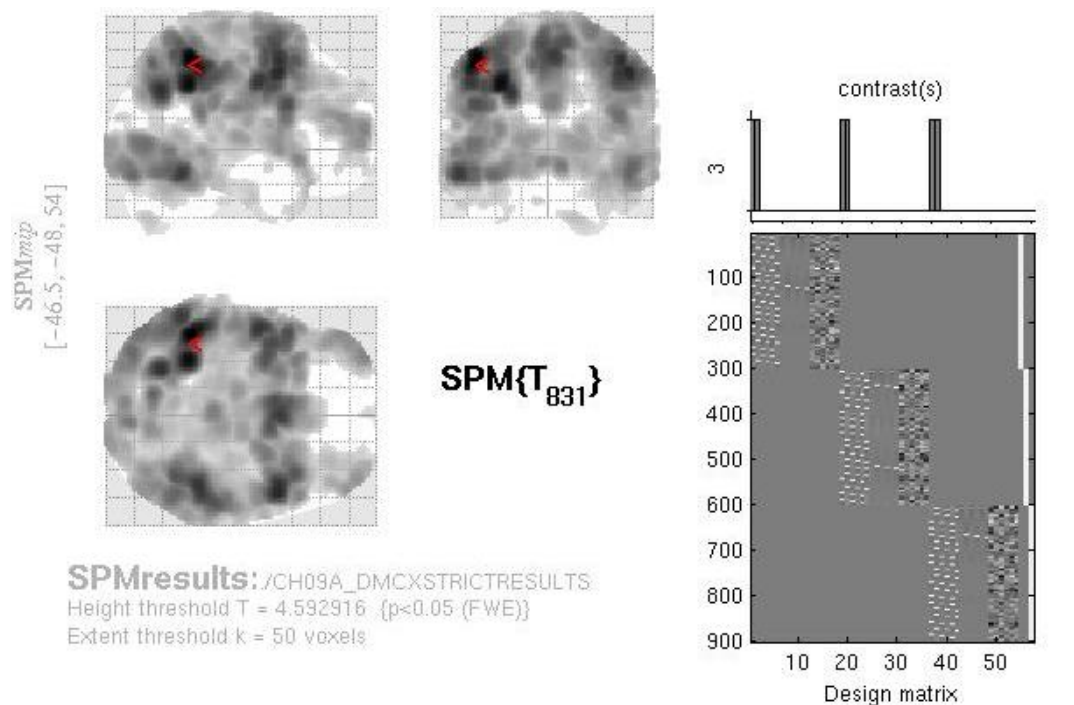
An example of the individual participant level results is presented for participant CH09 at baseline.

6.2.1 OVERALL EFFECTS OF ENCODING vs. BASELINE (ALL TRIALS)

At a conservative significance threshold, correcting for family wise error (FWE) $P_{FWE} < 0.05$ and extent threshold $k = 50$ voxels, examination of the statistical parametric map (SPM) demonstrated significant activations in fronto-parietal areas previously identified as active during encoding in similar digit span tasks²⁶ (Figure 6-4).

6.2.2 CHUNKING EFFECTS

In contrast to previous work examining chunking in young participants^{24 26}, there were no fronto-parietal regions demonstrating increased activation for the structured > random trials contrast, with a liberal significance threshold of $p < 0.01$ uncorrected (Figure 6-5). However the opposite contrast (random > structured) revealed a cluster of voxels demonstrating increased activation ($x = -46, y = -30, z = 61$; $x = -58, y = -19, z = 43$, and $x = -16, y = -40, z = 73$) significant at the cluster level ($p_{FWE} = 0.02$), (Figure 6-6).



Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_E)	p_{uncorr}			
0.000	8	0.000	0.000	1554670	0.000	0.000	0.000	22.65	Inf	0.000	-46	-48	54
						0.000	0.000	21.26	Inf	0.000	-32	-49	39
						0.000	0.000	19.00	Inf	0.000	49	8	46
		0.000	0.007	406	0.001	0.000	0.000	7.03	6.92	0.000	50	-10	-30
		0.000	0.007	445	0.001	0.000	0.000	6.84	6.74	0.000	15	-76	-45
						0.017	0.352	4.86	4.82	0.000	30	-66	-50
		0.009	0.477	51	0.174	0.000	0.005	5.78	5.72	0.000	27	-94	18
		0.005	0.461	77	0.100	0.001	0.023	5.48	5.43	0.000	-27	-7	-39
						0.003	0.076	5.22	5.18	0.000	-33	-12	-35
						0.006	0.129	5.10	5.06	0.000	-33	4	-47
		0.005	0.461	78	0.098	0.001	0.033	5.40	5.35	0.000	0	66	33
		0.009	0.477	50	0.178	0.002	0.038	5.37	5.32	0.000	-9	-28	-35
		0.006	0.477	66	0.125	0.002	0.049	5.32	5.27	0.000	-33	-21	-24

table shows 3 local maxima more than 8.0mm apart

Height threshold: $T = 4.59$, $p = 0.000$ (0.050)
 Extent threshold: $k = 50$ voxels, $p = 0.178$ (0.009)
 Expected voxels per cluster, $\langle k \rangle = 29.317$
 Expected number of clusters, $\langle c \rangle = 0.01$
 FWEp: 4.593, FDRp: 5.316, FWEc: 1, FDRc: 406

Degrees of freedom = [1.0, 831.0]
 FWHM = 15.2 15.3 12.0 mm mm mm; 10.1 10.2 8.0 {voxels}
 Volume: 1792436 = 531092 voxels = 608.7 resels
 Voxel size: 1.5 1.5 1.5 mm mm mm; (resel = 826.93 voxels)

Figure 6-4: SPM of all trials during encoding phase of digit span task.

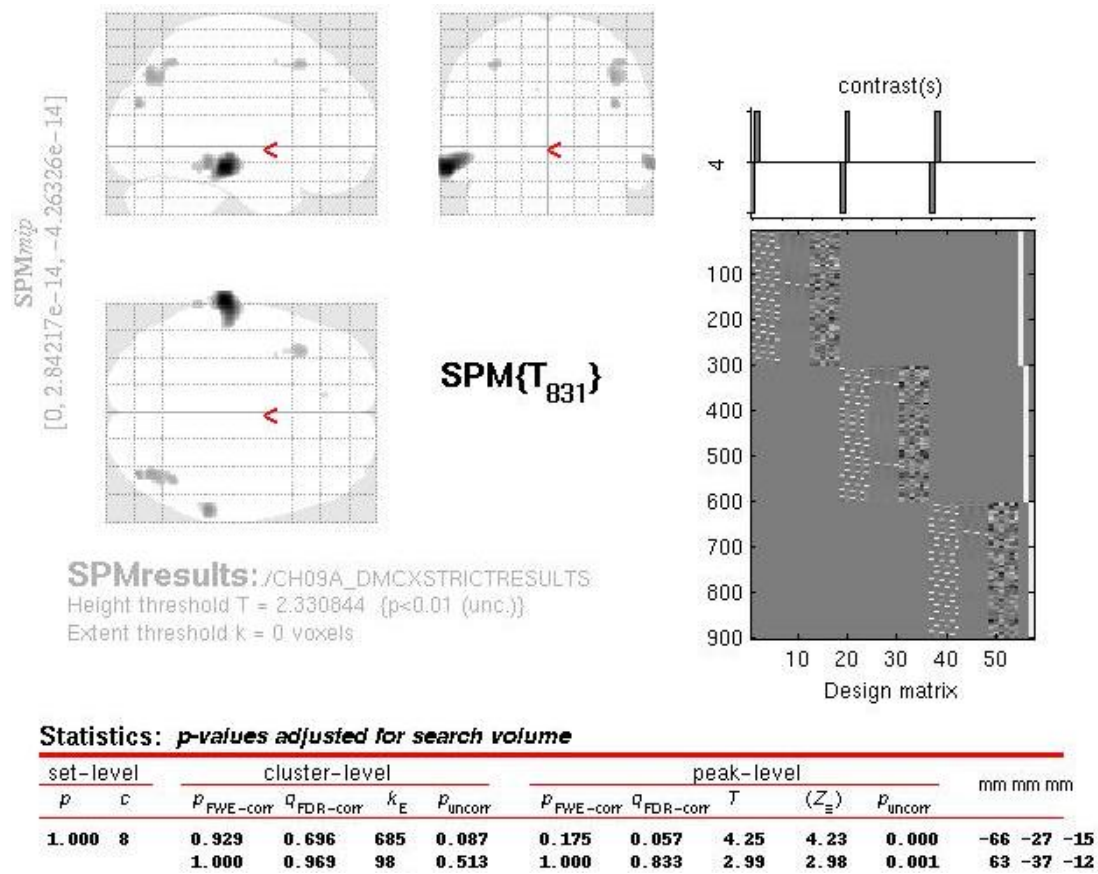


Figure 6-5: SPM of structured trials>random trials contrast.

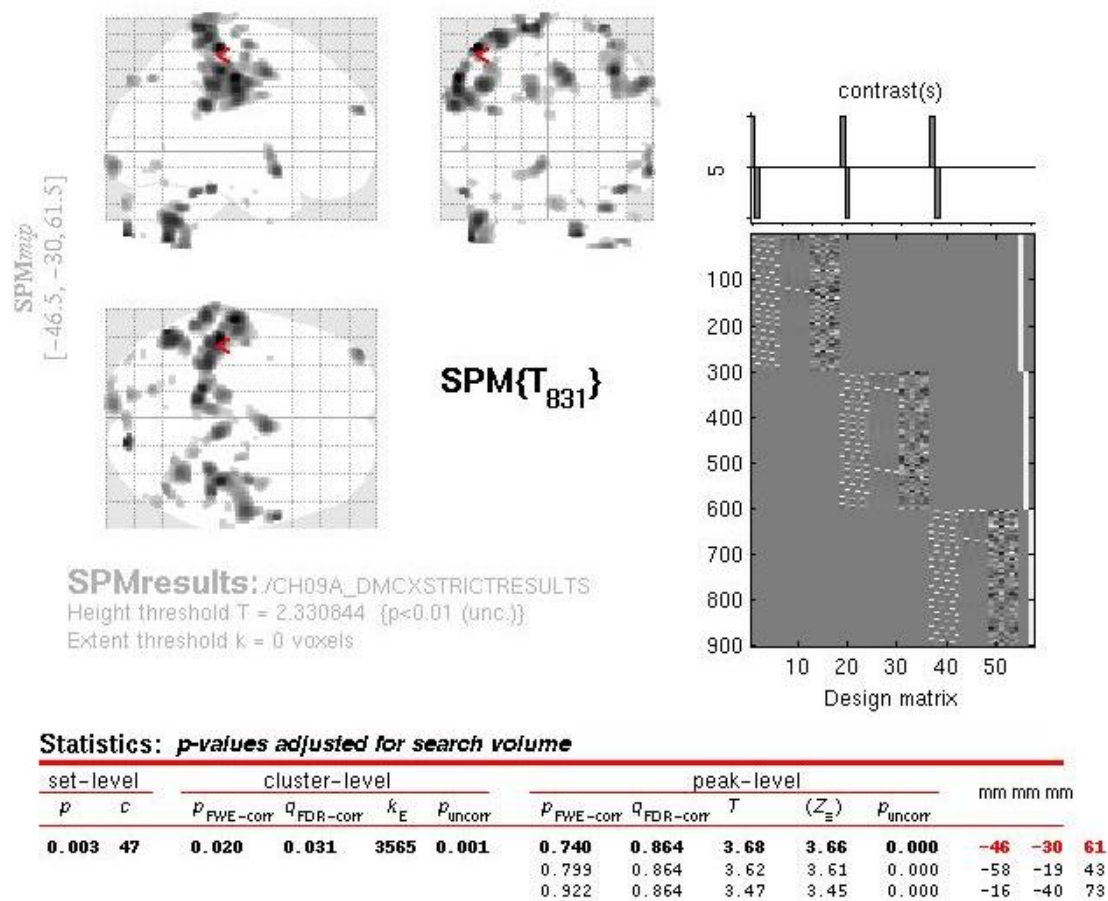


Figure 6-6: SPM for random > structured trials contrast, showing significant cluster level results.

6.3 SECOND LEVEL - GROUP ANALYSIS

Second level analyses followed an *a priori* hypothesis-driven approach based on previous studies demonstrating significant effects of chunking within dorso-lateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC). Results are presented as follows.

- 1) ROI (Region Of Interest) definition
- 2) Overall effects across all ROIs
- 3) Effects in individual ROI areas if significant overall effects seen.
- 4) Whole brain analysis at a liberal significance threshold to examine for further areas of interest

6.3.1 REGION OF INTEREST (ROI) DEFINITION

Bilateral DLPFC and PPC ROIs were defined from the study group data set. This was to allow for the anticipated task related functional differences between AD participants used in the current study and healthy young populations examined in previous studies^{24 26 27}.

ROI were defined by averaging across all groups and conditions and examining the SPM of the overall positive effect of task. As shown in Figure 6-7 and Figure 6-8, several voxels were significant with a conservative threshold of $p_{FWE} < 0.001$, including areas in the frontal and parietal lobes.

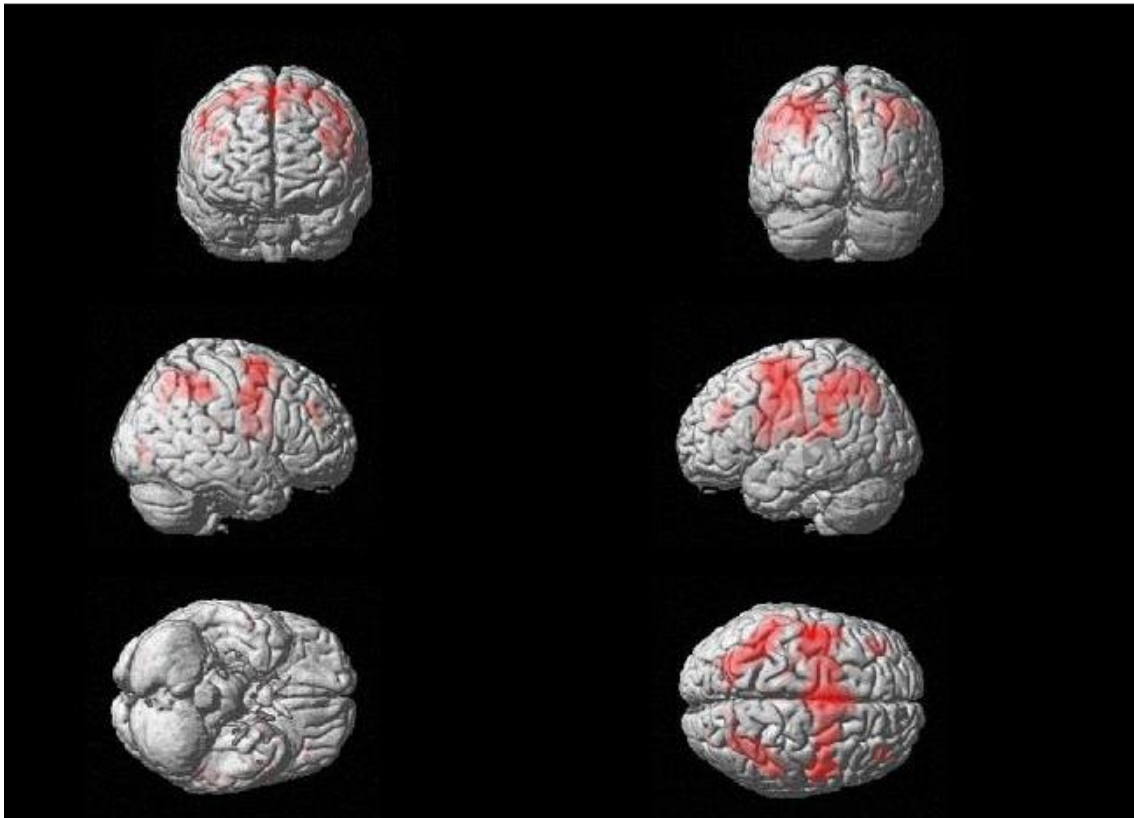


Figure 6-7: Overall positive effect of condition, at $p < 0.001$, rendered on a single participant template from SPM8.

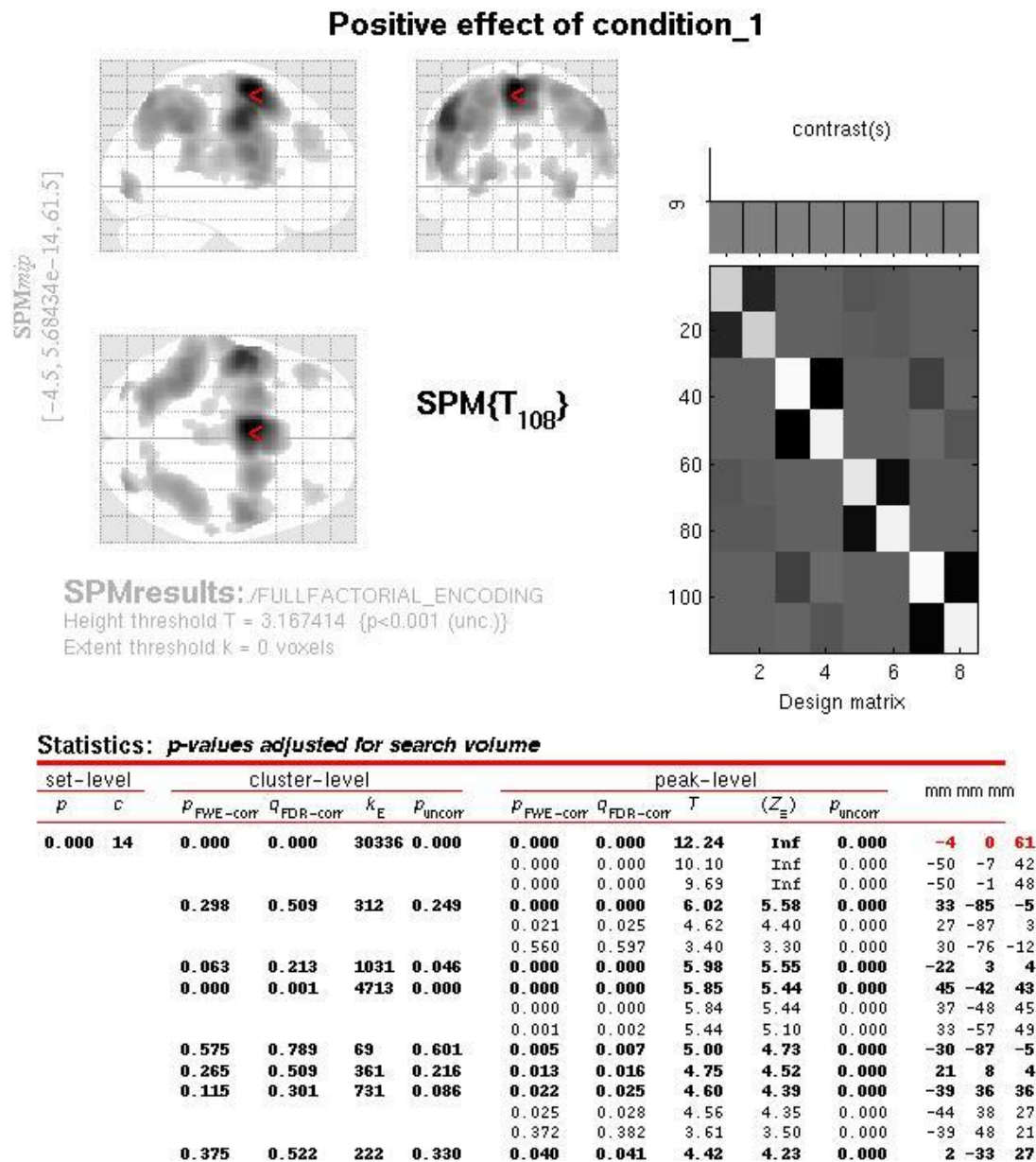


Figure 6-8: SPM of positive effect of condition contrast
Significance threshold of $p < 0.001$ (uncorrected). Results for voxels reaching significance with $p_{FWE} < 0.05$ are shown.

The contrasts of interest (time x group interactions) are orthogonal to the positive effect of task data used to identify ROIs, so should be free from bias. However, as a secondary sensitivity analysis, ROIs from a recently published iteration of the multiple demands network were also examined¹⁷⁶ for comparison with the study-defined ROIs. These were chosen rather than the original Bor et al ROIs²⁶ as they represent a more up to date iteration of networks of regions involved in similar strategy performance, and were taken from data from older participants, and therefore may be more appropriate to the current study population (see sensitivity analyses 6.4.1.1).

The coordinates of the defined ROI from the current study data are shown in Table 6-4 and Figure 6-9.

REGION	COORDINATES (x y z)
	ROI defined as 10mm ³ sphere around this central point
RIGHT DLPFC	39, 43, 33
LEFT DLPFC	-39, 36, 36
RIGHT PARIETAL CORTEX	46 , -40, 42
LEFT PARIETAL CORTEX	-37, -45, 37

Table 6-4: Defined ROIs from group F contrast of positive effects of condition.

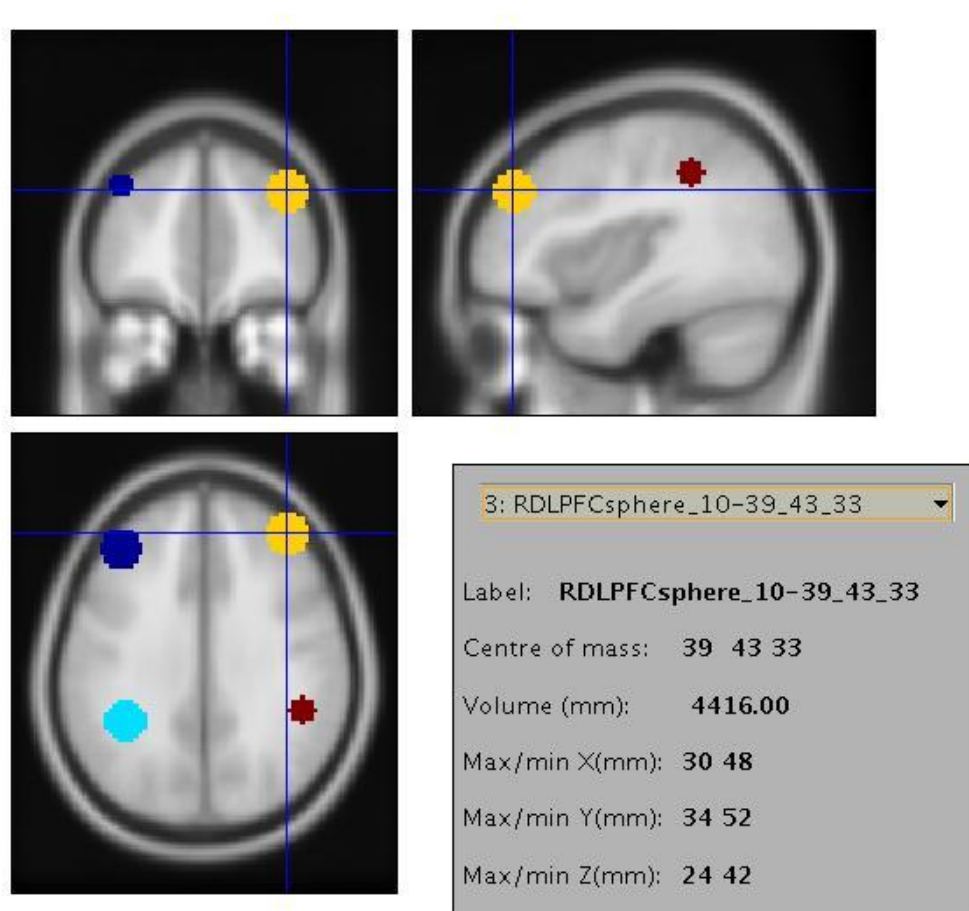


Figure 6-9: Locations of the 4 defined ROI, crosshairs are on the RDLPFC ROI.

6.3.2 OVERALL EFFECTS ACROSS ALL ROIs

The β values produced from each of the factors in the model were estimated for each ROI using the MarsBar toolbox in SPM8¹⁷⁰. These β values were exported into Microsoft excel and SPSS and assessed for normality and homogeneity of variance. As the data was not normally distributed, due to an outlier in each group, the data was winsorized, replacing the outliers with exact values of the mean – 2.5 SD, which effectively normalised the data. Analyses of the non-winsorized data are reported as part of the sensitivity analyses in 6.4. A mean β value across all 4 ROIs was calculated for each participant. These individual values were then averaged across each group. Change in β value by time was calculated as (post – pre) for each group and trial type. Overall change was calculated by averaging across both trial types. This gave a single mean and SD for change in β value for each group, averaged across ROI and trial type (Table 6-5 and Figure 6-10). The β values estimated by SPM8 don't strictly represent BOLD signal or functional activation, as they are estimates of the contribution of the conditions of interest to the observed effects calculating using the GLM. However in the interests of clarity, β values will be classified in charts and tables as 'fMRI response'.

	Mean change in fMRI response (post- pre intervention)	SD
CONTROL	1.03	2.20
TRAIN	-0.58	2.17

Table 6-5: Means (SD) of change in β value (fMRI response) across all 4ROI and trial type.

An independent T test revealed a near-significant difference in activation change between groups across this network ($t(27) = 1.975$, $p = 0.059$ (2-tailed)).

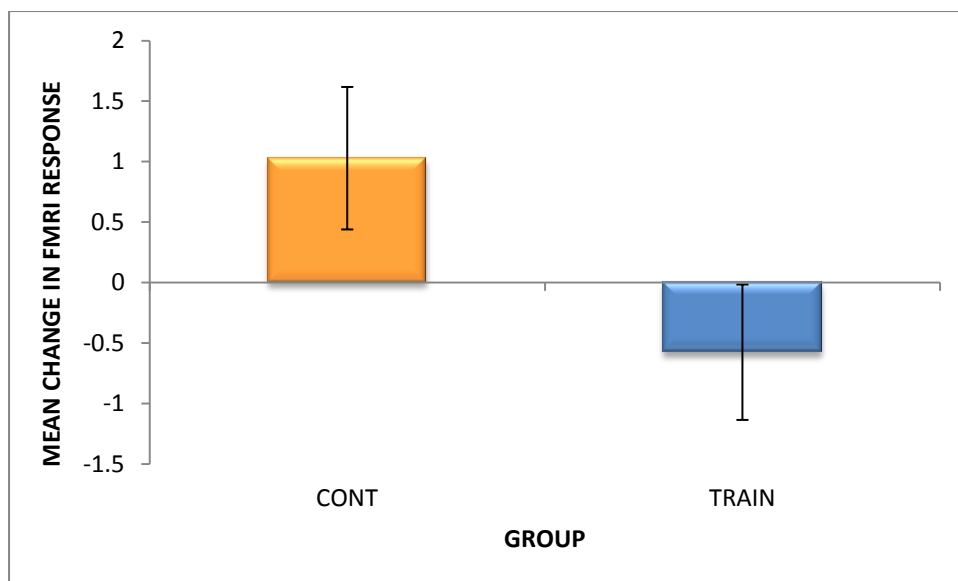


Figure 6-10: Overall mean change in fMRI response
This is the fMRI response averaged across all 4 ROIs for each participant for all trials. Error bars are SEM. The group difference approaches significance ($p = 0.059$).

As the behavioural results demonstrated that chunking training affected performance on structured trials more than random trials, the change in activation during performance on structured trials alone was examined. An independent T test demonstrated a significant difference between groups ($t(27) = 2.32$, $p = 0.028$ (2-tailed)), (Table 6-6 and Figure 6-11).

	Mean change in fMRI response (post- pre intervention)	SD
CONTROL	1.16	2.32
TRAIN	-0.78	2.17

Table 6-6: Mean change in fMRI response for structured trials
The group difference is significant ($p = 0.028$)

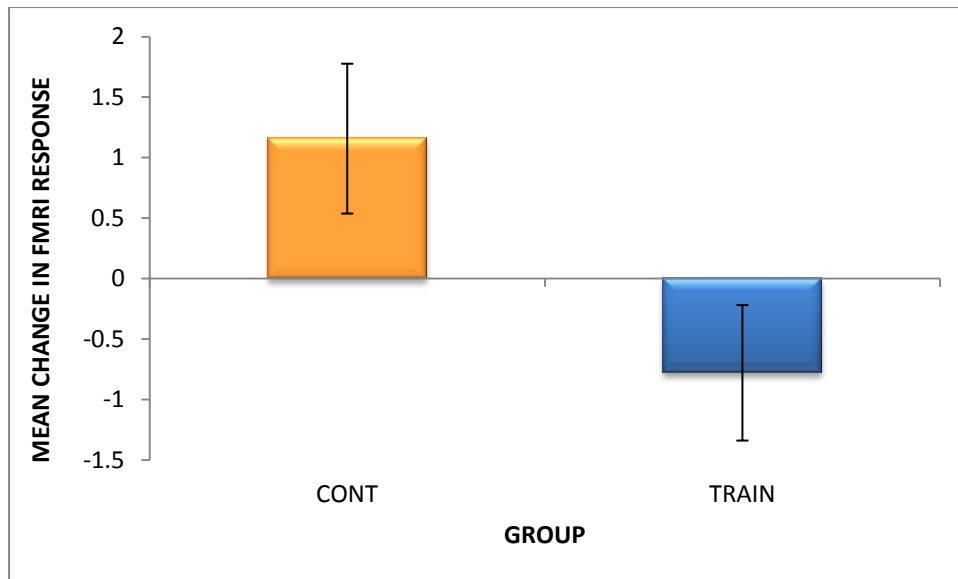


Figure 6-11: mean change in fMRI response across ROIs with structured trials
Error bars are SEM. The group difference is significant ($p = 0.028$).

As the overall effects were approaching significance, repeated measures analyses were conducted to examine for significant main effects and interactions between group and time, trial type, and ROI.

6.3.3 ANALYSES OF INDIVIDUAL ROIs

Mean β values and event types were entered into a repeated measures ANOVA. Within participant factors were time (pre vs. post), trial type (structured vs. random), ROI (DLPFC vs. PC) and hemisphere (right vs. left), with group as the between participants factor. Significant and near significant main effects and interactions are shown in Table 6-7. No other main effects or interactions were significant.

INTERACTION	F	Sig.(p)
TIME x GROUP	3.899	0.059
ROI x HEMISPHERE	4.211	0.050
TIME x TRIAL x HEMISPHERE	5.422	0.028
TIME x ROI x HEMISPHERE x GROUP	4.232	0.049
TRIAL x ROI x HEMISPHERE x GROUP	3.775	0.063
TIME x TRIAL x ROI x HEMISPHERE	6.989	0.013

Table 6-7: Significant and borderline significant main effects and interactions.

To further examine these significant complex interactions, separate repeated measures ANOVAs were conducted for each ROI and trial type. For structured trials there was a significant interaction between time x group ($F(1, 27) = 5.403$, $p = 0.028$) and a significant time x ROI x hemisphere x group

interaction ($F(1, 27) = 5.030, p = 0.033$), and no other significant main effects or interactions. For random trials there was a significant ROI x hemisphere interaction ($F(1, 27) = 4.562, p = 0.042$), and no other significant main effects or interactions. Therefore further ANOVAs were conducted with each ROI individually examining each trial type separately.

6.3.3.1 RIGHT DORSOLATERAL PREFRONTAL CORTEX

A repeated measures ANOVA, with time and trial type as within participants factors and group as the between participants factor, revealed a time x group interaction approaching significance ($F(1, 27) = 3.854, p = 0.060$). There were no other significant main effects or interactions. (Table 6-8, Figure 6-12 and Figure 6-13)

MAIN EFFECTS	F	Sig.(p)
TIME	0.373	0.546
TRIAL	1.228	0.278
GROUP	0.091	0.766
INTERACTIONS:		
TIME x GROUP	3.854	0.060
TRIAL x GROUP	0.007	0.934
TIME x TRIAL	2.164	0.153
TIME x TRIAL x GROUP	0.385	0.540

Table 6-8: ANOVA results for RDLPFC.

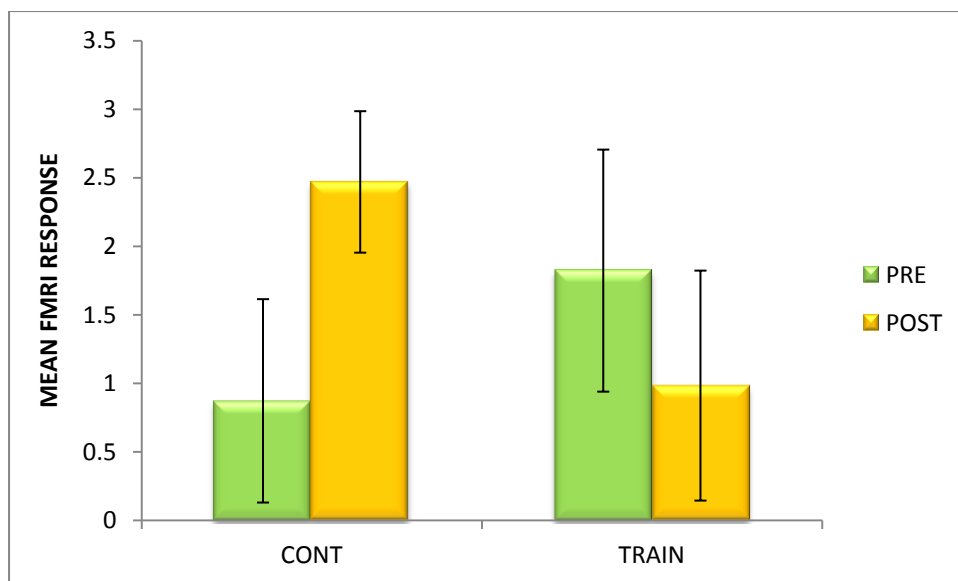


Figure 6-12: RDLPFC: Mean fMRI response from all trials at each time point for the control and training groups. Error bars are SEM.

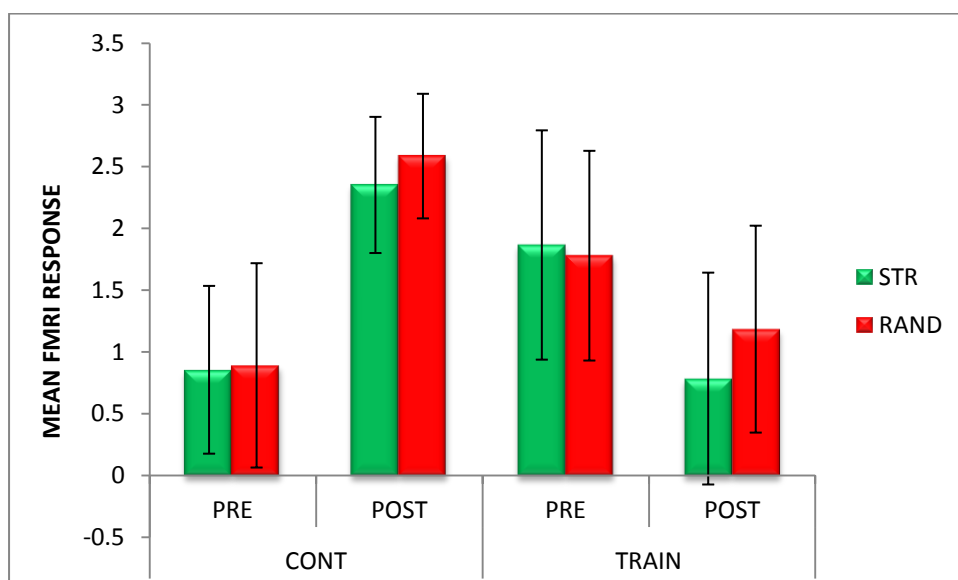


Figure 6-13: RDLPFC: Mean fMRI response by trial type and group. Error bars are SEM

Therefore the effect of training on mean fMRI response approached significance, with training resulting in reduced activation in the RDLPFC, compared to increased activation seen in the control group.

Examining each trial type separately; for structured trials only, there was a significant time x group interaction ($F(1, 27) = 4.422, p = 0.045$), but no main effects of time or group.

For random trials only, the time x group interaction was non significant ($F(1, 27) = 3.133, p = 0.088$), and there were no main effects of time or group.

6.3.3.2 LEFT DORSOLATERAL PREFRONTAL CORTEX

A repeated measures ANOVA was conducted on LDLPFC data with time (pre vs. post) and trial type (str vs. rand) as the within participants factors and group as the between participants factor.

There were no significant main effects of time ($F(1, 27) = 0.534, p = 0.471$), trial type ($F(1, 27) = 2.458, p = 0.129$) or group ($F(1, 27) = 0.024, p = 0.879$). There were also no significant group x time, or group x trial x time interactions (Table 6-9).

MAIN EFFECTS	F	Sig.(p)
TIME	0.534	0.471
TRIAL	2.160	0.153
GROUP	0.024	0.879
INTERACTIONS		
TIME x GROUP	2.160	0.153
TRIAL x GROUP	0.418	0.523
TIME x TRIAL	0.440	0.513
TIME x TRIAL x GROUP	0.361	0.553

Table 6-9: ANOVA results for LDLPFC.

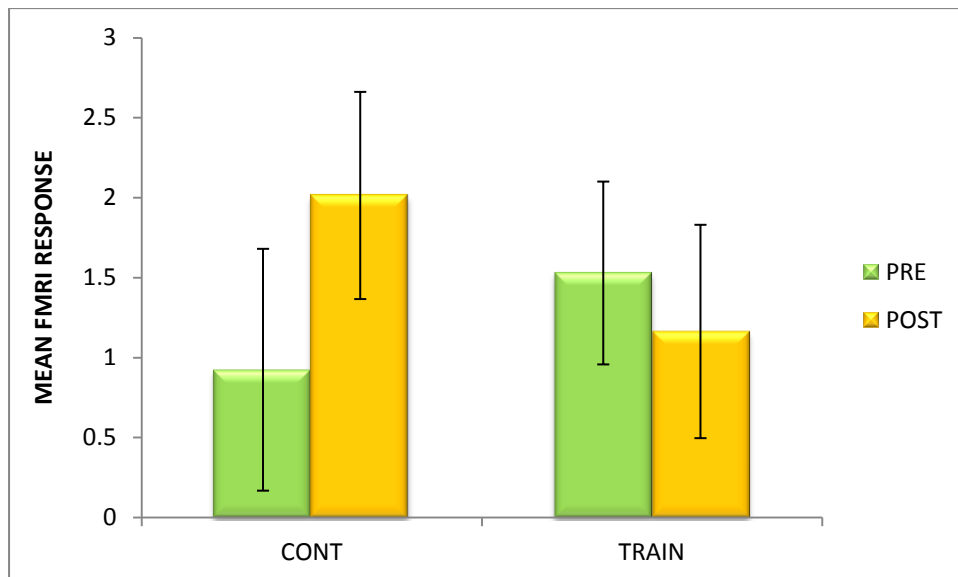


Figure 6-14: LDLPFC: Mean fMRI response from all trials at each time point for the control and training groups. Error bars are SEM.

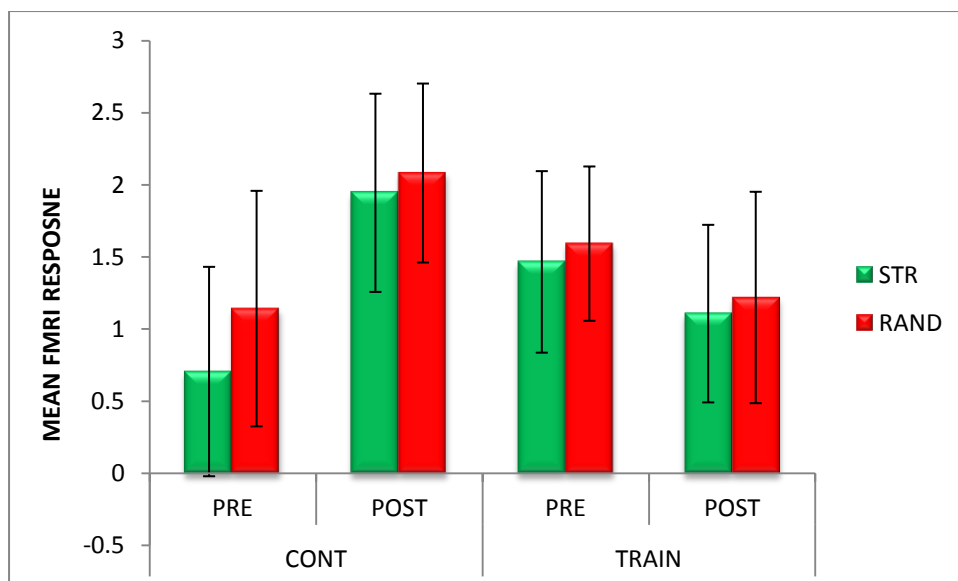


Figure 6-15: LDLPFC: Mean fMRI response by trial types, groups and time. Error bars are SEM.

Examining each trial type separately, revealed that there were no significant main effects or interactions with either trial type.

Although the differences were non-significant, training resulted in reduced activation in the LDLPFC, compared to increased activation seen in the control group, a similar pattern to the RDLPFC.

6.3.3.3 LEFT PARIETAL CORTEX

A repeated measures ANOVA was conducted on LPC data with time (pre vs. post), and trial type (str vs. rand) as within participants factors and group as the between participants factor. As shown in Table 6-10, there were no significant main effects of time or trial type, or between participants effect of group. There was no significant interaction between time and group, however the interaction between time x trial type x group was significant ($F(1, 27) = 4.647, p = 0.040$).

MAIN EFFECTS	F	Sig.(p)
TIME	< 0.001	0.987
TRIAL	2.170	0.152
GROUP	0.139	0.713
INTERACTIONS		
TIME x GROUP	2.521	0.124
TRIAL x GROUP	0.053	0.820

TIME x TRIAL	0.032	0.859
TIME x TRIAL x GROUP	4.647	0.040

Table 6-10: LPC ANOVA results

Figure 6-16 and Figure 6-17, show the same pattern of training effects on activation seen in the DLPFC, with training resulting in a decrease in activation compared to an increase in the control group. Additionally, in the LPC there was a significant differential effect of training on activation between structured and random trials.

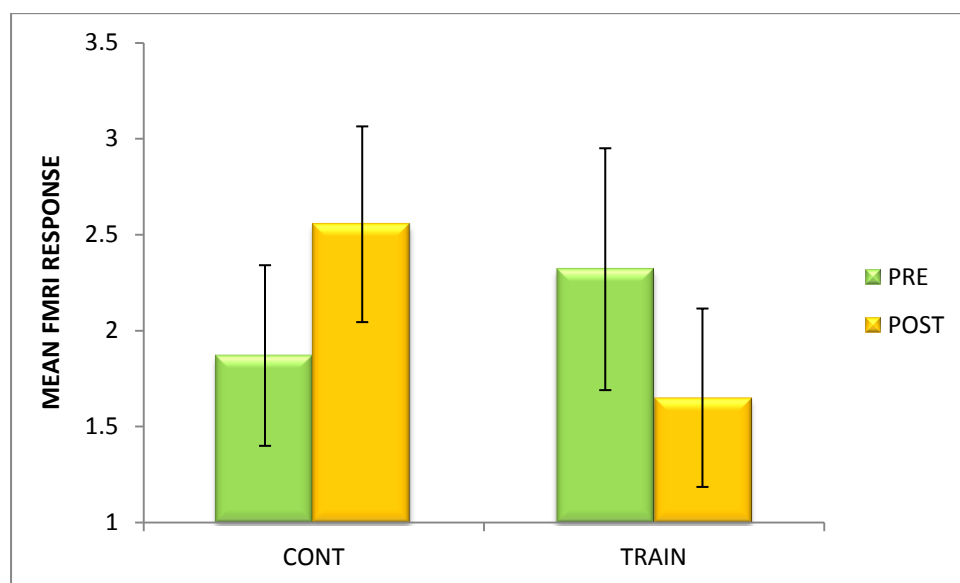


Figure 6-16: LPC: Mean fMRI response from all trials at each time point for the control and training groups. Error bars are SEM.

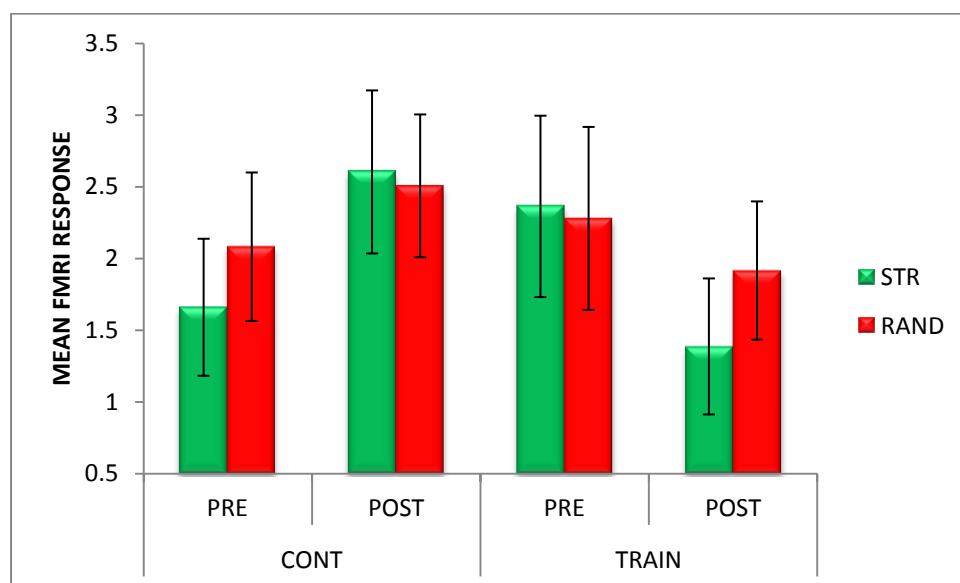


Figure 6-17: LPC: Mean fMRI response by trial types, group and time. Error bars are SEM.

Examining structured trials only revealed a significant time x group interaction ($F(1, 27) = 4.604$, $p = 0.041$) and no significant main effects of time or group. No significant main effects or interactions were found with only random trials.

6.3.3.4 RIGHT PARIETAL CORTEX

A repeated measures ANOVA was conducted on RPC data with time (pre vs. post), and trial type (str vs. rand) as within participants factors and group as the between participants factor. There were no significant main effects of time, trial type or group, and no significant interactions (Table 6-11, Figure 6-18 and Figure 6-19).

MAIN EFFECTS	F	Sig.(p)
TIME	0.171	0.683
TRIAL	0.818	0.374
BETWEEN PARTICIPANTS-GROUP	0.069	0.795
INTERACTIONS		
TIME x GROUP	2.429	0.131
TRIAL x GROUP	0.475	0.497
TIME x TRIAL	0.042	0.840
TIME x TRIAL x GROUP	2.010	0.168

Table 6-11: RPC ANOVA results

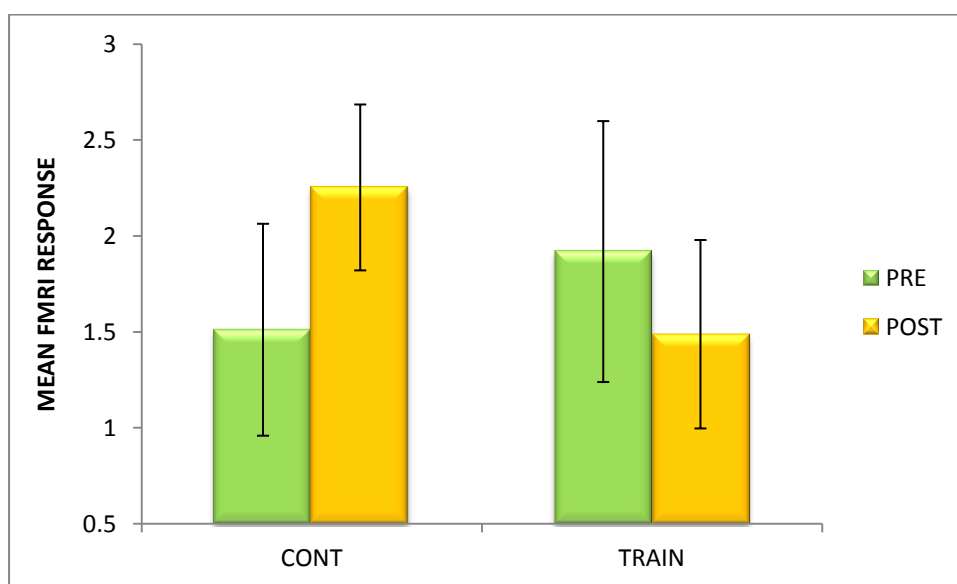
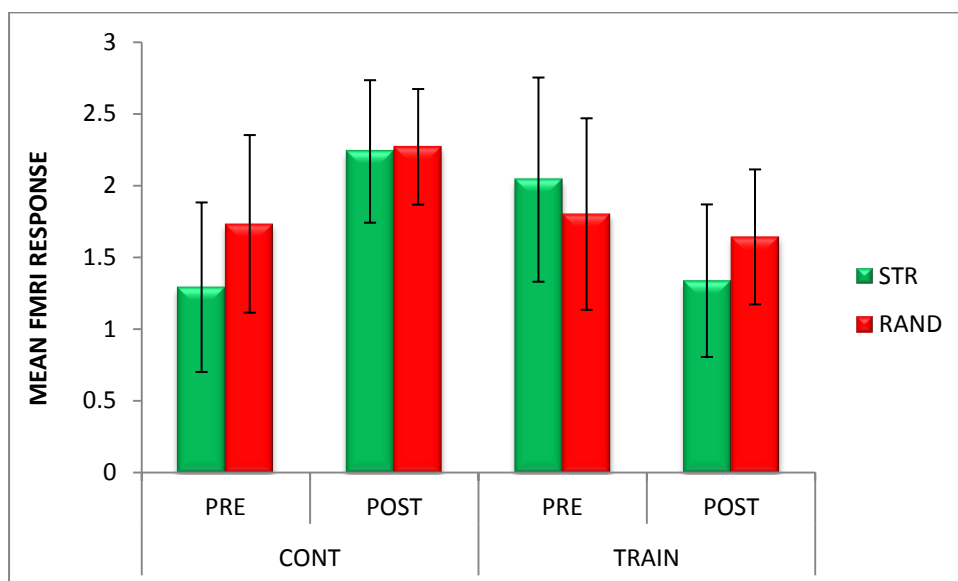


Figure 6-18: RPC: Mean fMRI response from all trials at each time point for the control and training groups. Error bars are SEM.



. Figure 6-19: RPC: Mean fMRI response by trial types, group and time. Error bars are SEM

Examination of structured trials revealed a near significant time x group interaction ($F(1, 27) = 4.072$, $p = 0.054$) and no main effects of time or group. There were no significant main effects or interactions when random trials were examined.

These results demonstrate a similar pattern of training - related reduced activation in all four regions of interest as a result of training compared with activation in all four regions in the control group. However this only reached significance with structured trials in the RDLPFC and LPC.

6.4 SENSITIVITY ANALYSIS

6.4.1 SENSITIVITY ANALYSIS- ANALYSIS OF ALL TRIALS

The basic model described in the methods chapter (section 4.4.1), examined all correct and incorrect trials together as a single event of interest. The same 4 ROIs were examined from the β values estimated from this model.

As described in 6.3.2, the data was winsorized and a mean β value across all 4 ROI was calculated for each participant. These individual values were then averaged across each group. Change in β value by time was calculated as (post – pre) for each group and trial type. Overall change was calculated by averaging across both trial types. This gave a single mean and SD for change in β value for each group, averaged across ROI and trial type.

An independent T test revealed a mean difference in fMRI response across this network of 0.94 (SD = 1.80) in the control group and -0.35 (SD = 1.80) in the training group ($t(27) = 1.930$, $p = 0.064$ (2-tailed)). Therefore when all trials are examined irrespective of correct or incorrect response, the overall effect of training on the defined ROIs approached significance (Figure 6-20).

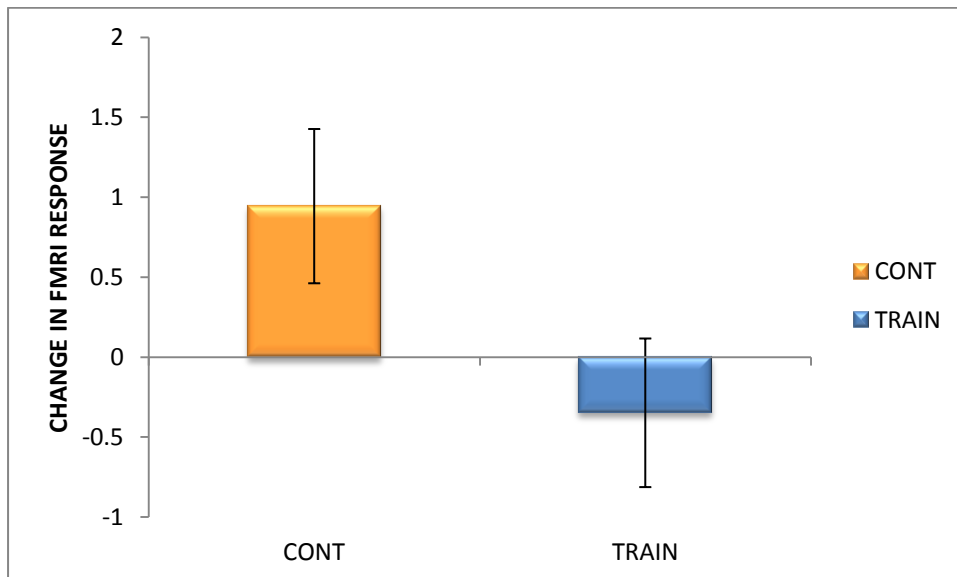


Figure 6-20: Mean change across all 4 ROI and trial types for basic model
Group difference $p=0.066$. Error bars are SEM.

Examination of each ROI independently with repeated measures ANOVAs also produced similar results to the main analysis, with a significant training effect (time x group) interaction seen in the RDLPFC, but not in the other ROIs (see Table 6-12 and Figure 6-21).

	LDLPFC	LPC	RDLPFC	RPC
MAIN EFFECTS	F (p)	F (p)	F (p)	F (p)
TIME	1.264 (0.271)	0.059 (0.811)	0.519 (0.477)	0.582 (0.452)
TRIAL	1.485 (0.234)	1.562 (0.222)	0.720 (0.404)	0.316 (0.579)
GROUP	0.031 (0.863)	0.555 (0.463)	0.078 (0.782)	0.294 (0.592)
INTERACTIONS				
TIME x GROUP	1.524 (0.228)	1.988 (0.170)	4.972 (0.034)	1.533 (0.226)
TIME x TRIAL x GROUP	1.978 (0.171)	2.766 (0.108)	3.142 (0.088)	3.452 (0.074)

Table 6-12: ANOVA results for all 4 ROI for analysis of all (correct and incorrect) trials.

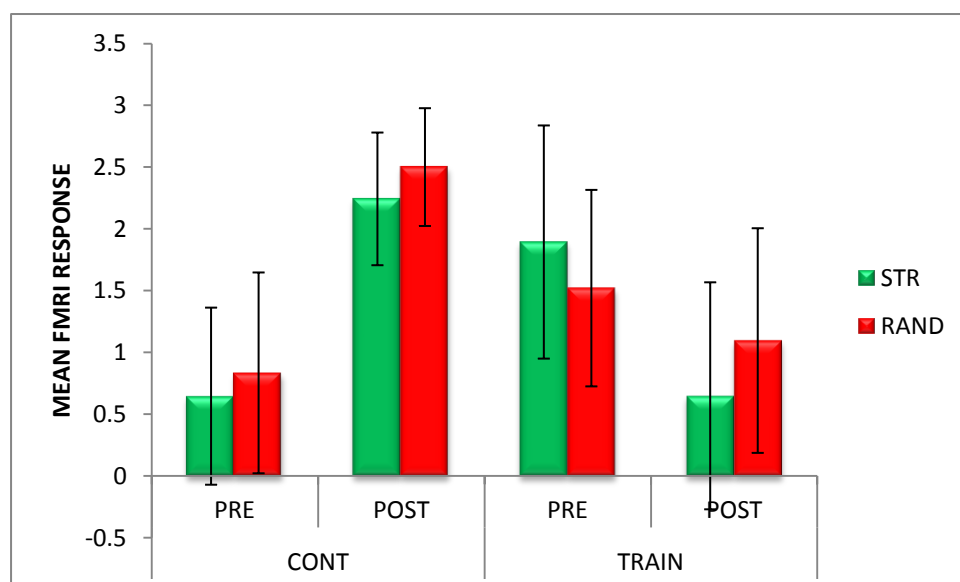


Figure 6-21: Mean fMRI response for RDLPFC for basic model
Both correct and incorrect trials examined, (time x group $p = 0.034$). Error bars are SEM.

Therefore, analysis of all trials irrespective of correct response produced similar results to the main analysis of only correct trials.

6.4.1.1 SENSITIVITY ANALYSIS- COMPARISON WITH MD ROIs

The contrasts of interest (time x group interactions) were orthogonal to the contrast used to define the ROI from our own participant group. However in order to provide further evidence for choice of these regions being valid and free from bias, the analysis was repeated using a network of regions recently identified as an important multiple demands (MD) network¹⁷⁶. These results are the latest iteration of previous work by Bor et al²⁷, and therefore supersede previous chunking – associated ROIs²⁶.

These MD ROIs were bilateral:

- 1) anterior frontal region (centre $x = \pm 21$, $y = 44$, $z = -9$)
- 2) anterior inferior frontal region (centre $x = \pm 35.1$, $y = 18.7$, $z = 2.64$)
- 3) inferior frontal region (centre $x = \pm 38.1$, $y = 26.3$, $z = 23.9$)
- 4) ACC/SMA (centre $x = \pm 5.65$, $y = 22.6$, $z = 38.7$)
- 5) inferior parietal cortex (centre $x = \pm 35.3$, $y = -58.3$, $z = 40.5$)

No data was available for right or left anterior frontal regions at the group level, therefore β values were estimated for the remaining four bilateral regions using MarsBar. (Figure 6-22).

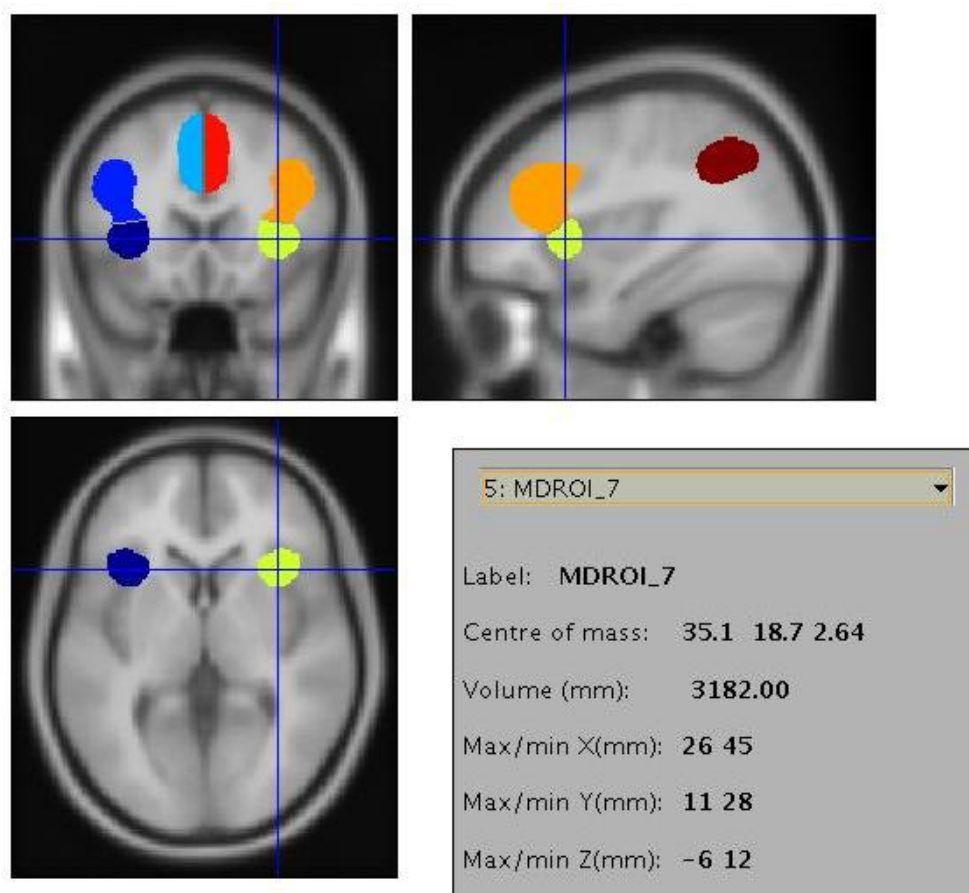


Figure 6-22: MD ROIs. Cross hairs show the Right anterior inferior region.

As the purpose of this analysis was to provide confirmation of the results derived from the study defined ROI, rather than investigate overall significance, these β values were winsorized and entered into separate repeated analyses ANOVAs for each ROI. Trial type and time were within participants factors with group as the between participants factor. As shown in Table 6-13, there were no significant main effects of time, and no significant time x group interactions for any of the ROI. However there was a significant time x trial type x group interaction in the right anterior inferior region (RAIFR) ($F(1, 27) = 5.565, p = 0.026$) and a time x trial x group interaction that neared significance in the left inferior parietal cortex (LIPC) ($F(1, 27) = 3.505, p = 0.072$). These represent areas in the RDLPFC and LPC, and are therefore similar to the defined ROIs from the present study that provided significant or near significant time x group, or time x trial x group interactions. In all regions a similar pattern was seen, with training resulting in a decrease in activation with time, compared to an increase in activation in the control group. These interactions are shown in Table 6-13, Figure 6-23, Figure 6-24 and Figure 6-25.

ROI	L AIFR	L IFR	L ACC	L IPC	R AIFR	R IFR	R ACC	R IPC
F (p)								
TIME	0.987 (0.329)	0.423 (0.521)	0.740 (0.397)	0.136 (0.715)	0.207 (0.653)	0.921 (0.346)	0.807 (0.377)	0.020 (0.888)
TIME x GROUP	0.902 (0.351)	1.588 (0.218)	1.140 (0.295)	2.247 (0.145)	1.091 (0.305)	2.428 (0.131)	1.518 (0.229)	2.552 (0.122)
TIME X TRIAL X GROUP	1.987 (0.170)	1.181 (0.287)	0.792 (0.381)	3.505 (0.072)*	5.565 (0.026)*	1.140 (0.295)	0.691 (0.413)	2.502 (0.125)
GROUP	0.05 (0.943)	0.066 (0.799)	0.320 (0.576)	0.347 (0.561)	0.069 (0.794)	0.154 (0.698)	0.311 (0.582)	0.444 (0.511)

Table 6-13: MD ROI: repeated measures ANOVA results of MD ROIs.

Within participants main effect of time and time x group interaction, and between participants effect of group are shown. *Significant and near significant results in bold.

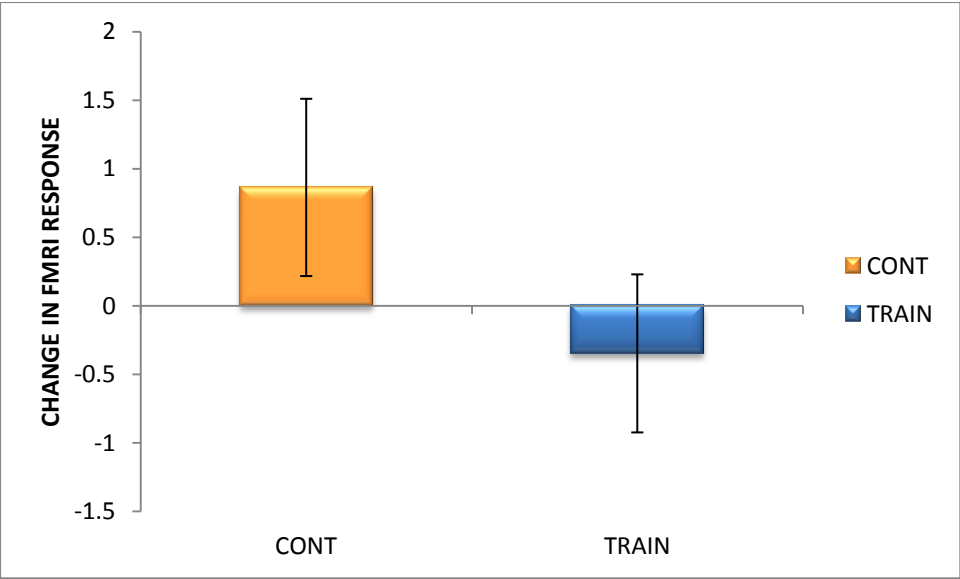


Figure 6-23: Change in fMRI response following training across all 8 MD ROIs and trial types.

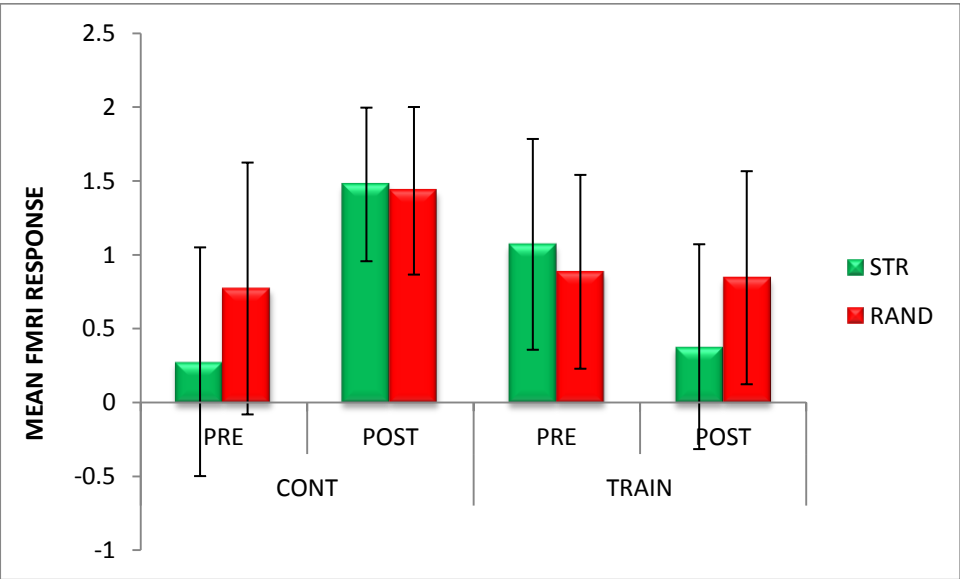


Figure 6-24: Mean fMRI response by group and time point in the RAIFO
Time x trial x group interaction is significant ($p=0.026$).

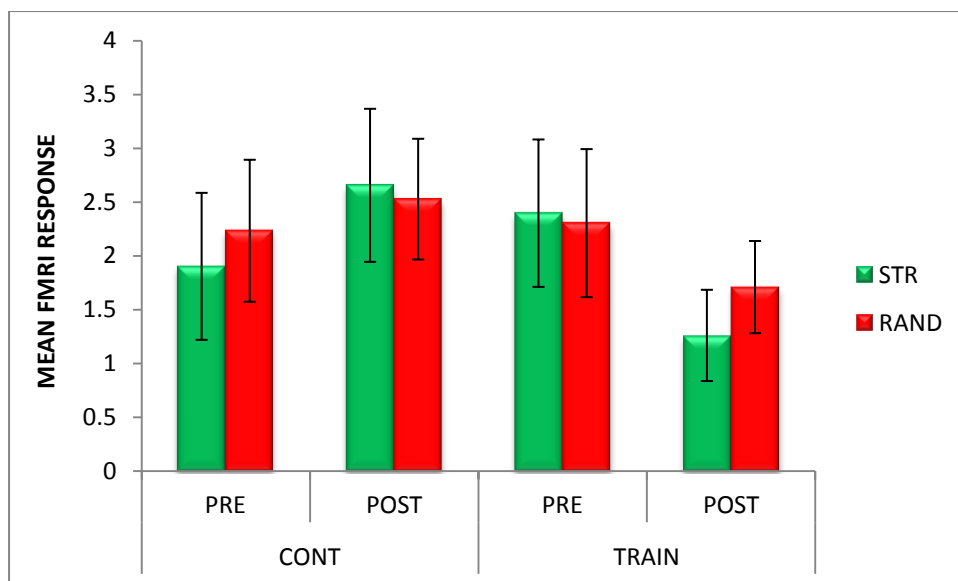


Figure 6-25: Mean fMRI response by group and time point in the LIPC.

6.4.1.2 ANALYSIS WITH NON - WINSORIZED DATA

As discussed in 6.3.2, the β values estimated in SPM8 for the ROIs were assessed for normality. As some of the ROI data was not normally distributed the data was winsorized to adjust outliers. Out of the 464 data points, only 8 were adjusted by this process, and all from one control and one training participant. The training participant's β values demonstrated a large reduction post training in the DLPFC ROIs, therefore they were consistent with the group data but of a greater magnitude that skewed the data.

Analysis of the overall change in fMRI response was conducted in the same manner as with the winsorized data. The mean β value across all 4 ROI was calculated for each participant. These individual values were then averaged across each group. Change in β value by time was calculated as post – pre for each group and trial type, and overall change was calculated by averaging across both trial types. This gave a single mean and SD for change in β value for each group, averaged across ROI and trial type (Table 6-14 and Figure 6-26). A Mann Whitney test revealed a significant group difference ($U = 60.0$, $z = -1.96$, $p = 0.050$ (2 – tailed)).

	Mean change in fMRI response (post- pre intervention)	SD
CONTROL	1.03	2.20
TRAIN	-0.68	2.38

Table 6-14: Mean change in fMRI response across all 4 ROIs using non-winsorized data.

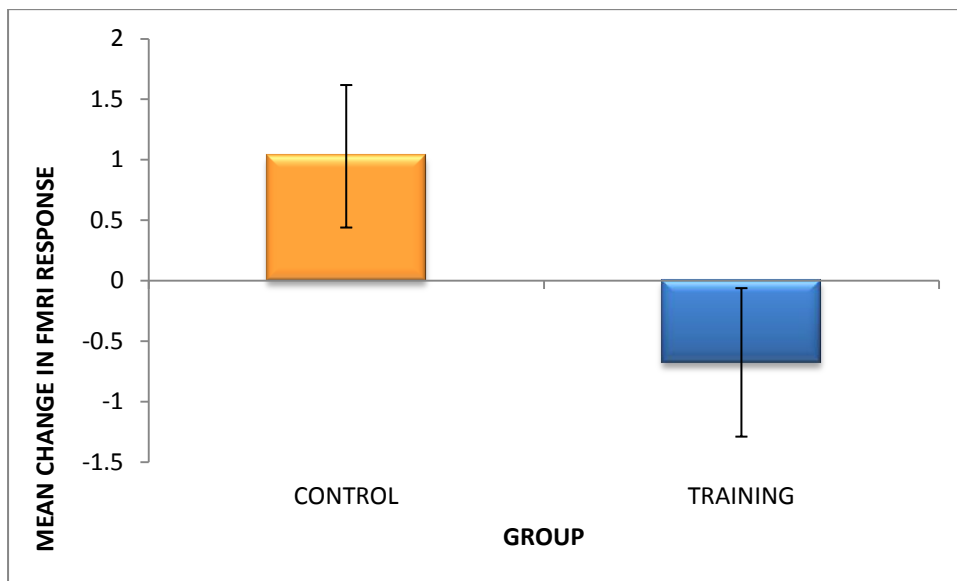


Figure 6-26: Mean change in fMRI response across all 4 ROI using non-winsorized data. Error bars are SEM. There is a significant group difference (Mann Whitney test, $p = 0.05$).

Repeated measures ANOVAs were conducted for each ROI individually. Trial type and time were within participants factors with group as the between participants factor. The results from the original data, including the outliers, revealed a similar pattern of results, with significant or near significant interactions in the RDLPFC (time x group $p = 0.049$) and LPC (time x trial x group $p = 0.065$). (Table 6-15, Figure 6-27 and Figure 6-28)

MAIN EFFECTS	LDLPFC F (p)	LPC F (p)	RDLPFC F (p)	RPC F (p)
TIME	0.366 (0.550)	0.06 (0.938)	0.091 (0.765)	0.175 (0.679)
TRIAL	2.323 (0.139)	2.323 (0.139)	1.301 (0.264)	0.881 (0.356)

GROUP	0.046 (0.831)	0.167 (0.686)	0.195 (0.662)	0.079 (0.781)
INTERACTIONS				
TIME x GROUP	2.366 (0.136)	2.201 (0.150)	4.265 (0.049)	2.403 (0.133)
TIME x TRIAL x GROUP	0.287 (0.597)	3.688 (0.065)	0.446 (0.510)	2.103 (0.159)

Table 6-15: Repeated measures ANOVA results for all ROIs, using non-winsorized data.

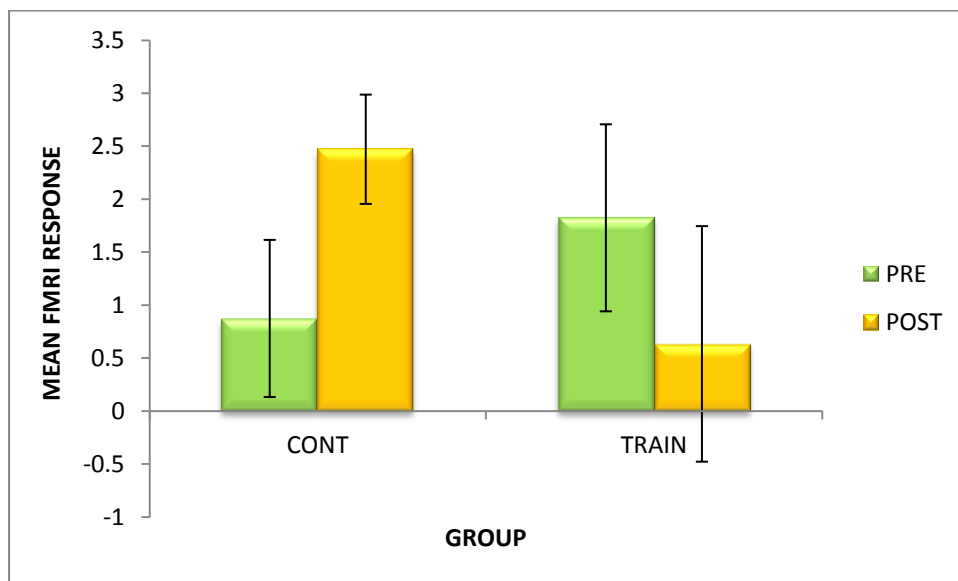


Figure 6-27: RDLPFC: Mean fMRI response across both trial types using non-winsorized data. Error bars are SEM. Time x group interaction is significant ($p = 0.049$)

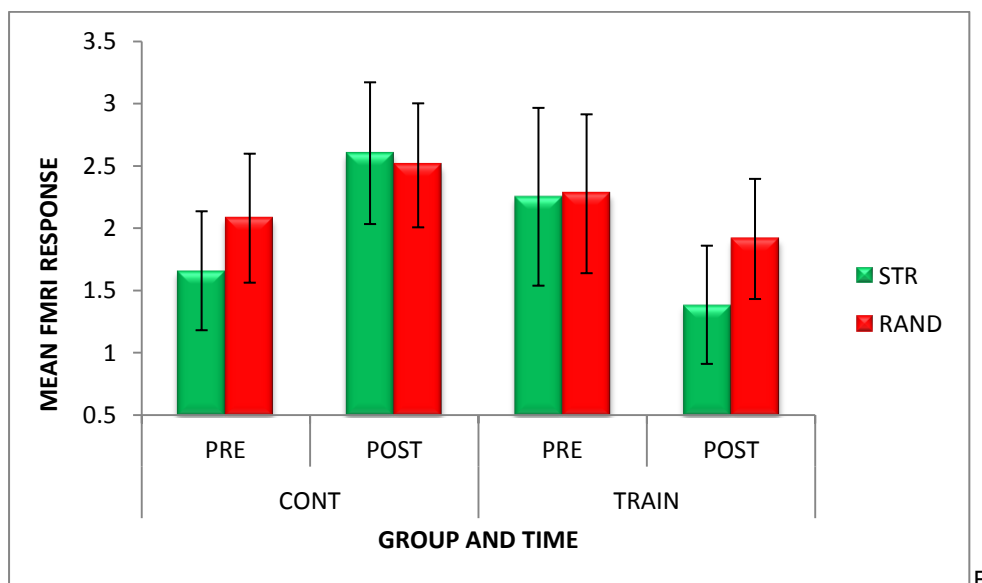


Figure 6-28: LPC: mean fMRI response for each trial type using non-winsorized data. Error bars are SEM. The time x trial x group interaction approaches significance ($p = 0.065$)

Therefore all three sensitivity analyses produce a consistent pattern of results. There was a decrease in fMRI response following training, compared with an increase in fMRI response in control participants. This training-related difference was consistently most significant in RDLPFC and LPC, with structured trials.

6.5 EFFECTS OF CHUNKING AT BASELINE

The contrast between structured and random trials was examined at baseline to identify whether the use of chunking led to any significant differences in activation, as has previously been reported in healthy young participants²⁶.

β values were averaged across the 4 ROIs for each individual, for each trial type separately.

A paired T test revealed no significant difference in activation between structured and random trials, when both groups were included in the analysis ($t(28) = -0.661$, $p = 0.514$ (2-tailed), Figure 6-29).

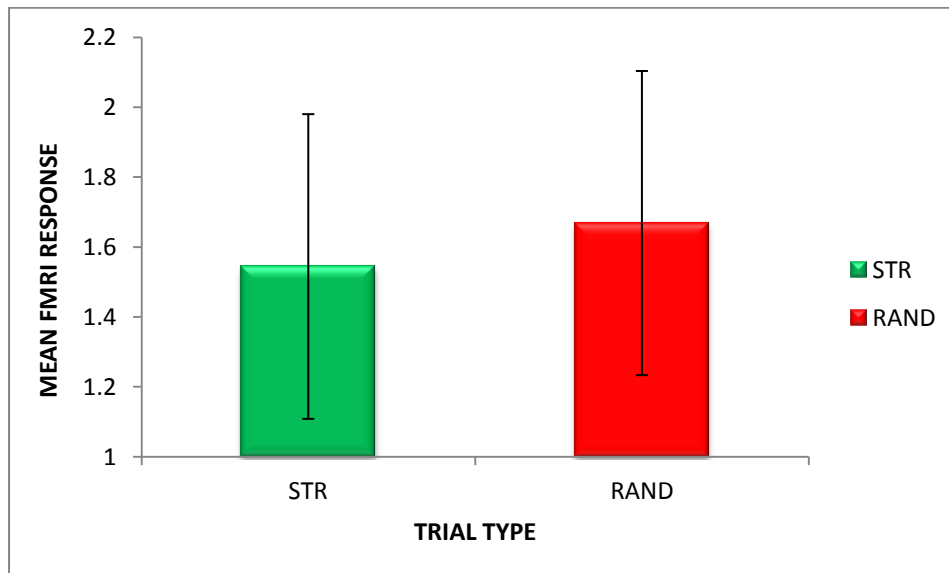


Figure 6-29: Mean fMRI response across all 4 ROI, for both groups combined at baseline. Error bars are SEM

In keeping with this, repeated measures analysis with trial type as a within participants factor and group as a between participants factor revealed no significant main effect of trial type ($F(1, 27) = 0.491$, $p = 0.490$), no significant main effect of group ($F(1, 27) = 0.493$, $p = 0.489$) and no significant interaction between trial type and group ($F(1, 27) = 1.171$, $p = 0.289$). (Figure 6-30).

Therefore, although there was a significant difference between performance on structured and random trials, this was not reflected in any underlying significant differences in activation in the ROIs.

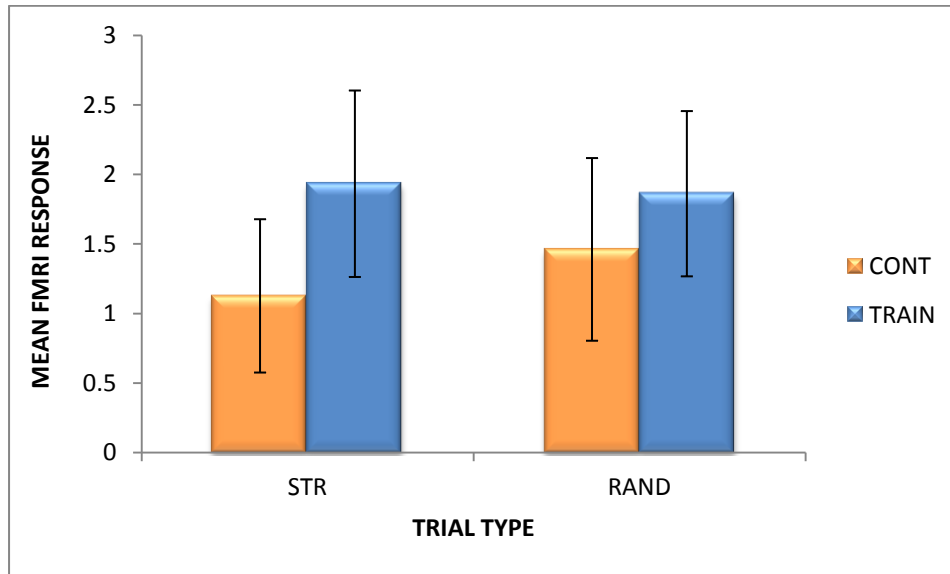


Figure 6-30: Mean fMRI response by trial type and group at baseline
Error bars are SEM.

6.5.1 EFFECT OF TRAINING ON CHUNKING

A value for chunking was calculated by (mean β value during structured trials – mean β value during random trials) in each ROI for each participant. The values were then averaged across all 4 ROIs to produce an overall chunking score. This was calculated at both pre- and post-intervention time points. A repeated measures ANOVA was then performed. There were no significant main effects of time ($F(1, 27) = 0.115$, $p = 0.738$), or group ($F(1, 27) = 0.107$, $p = 0.747$), and no significant interaction between time and group ($F(1, 27) = 2.249$, $p = 0.145$). As found in ANOVAs of individual ROIs, there was a significant change in fMRI response with chunking following training in the LPC ($F(1, 27) = 4.635$, $p = 0.040$) (Figure 6-31), and no other significant main effects or interactions for any of the other ROIs. Although mostly non-significant, the change in fMRI response with the chunking contrast is consistent with all training group results, which demonstrated that structured trials produced a greater reduction of activation following training than random trials in all ROIs.

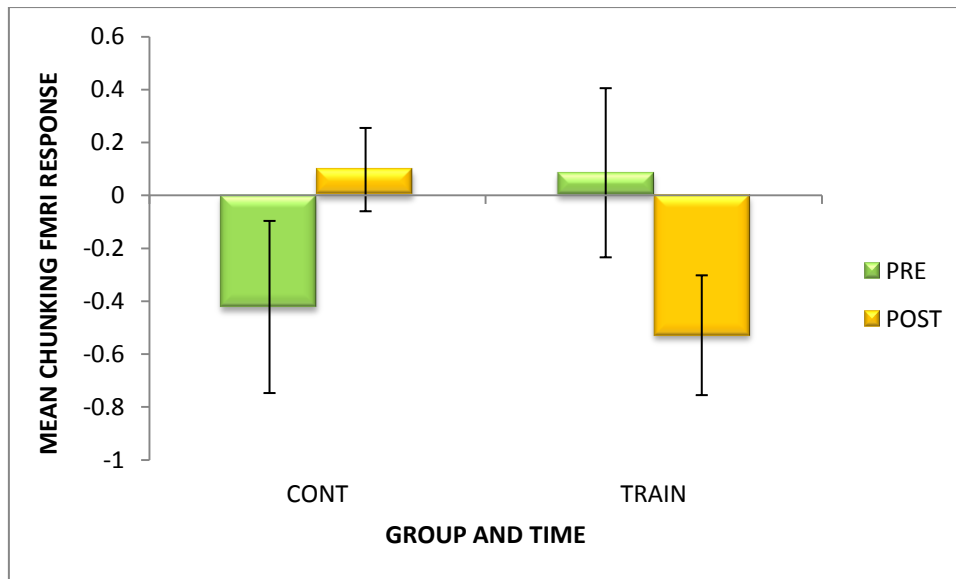


Figure 6-31: Mean fMRI response in LPC for chunking contrast (β value for structured – β value for random trials) at both time points and for both groups. The time x group interaction was significant ($p = 0.04$).

6.6 WHOLE BRAIN ANALYSIS

Results of whole brain analysis were also examined to identify any additional voxels or voxel clusters that significantly changed in level of activation, other than the defined ROIs.

6.7 EFFECTS OF TRAINING- TIME X GROUP CONTRASTS

The time by group contrast was examined for the whole brain, with a liberal threshold of $p = 0.01$ uncorrected, and an extent threshold of 5 voxels.

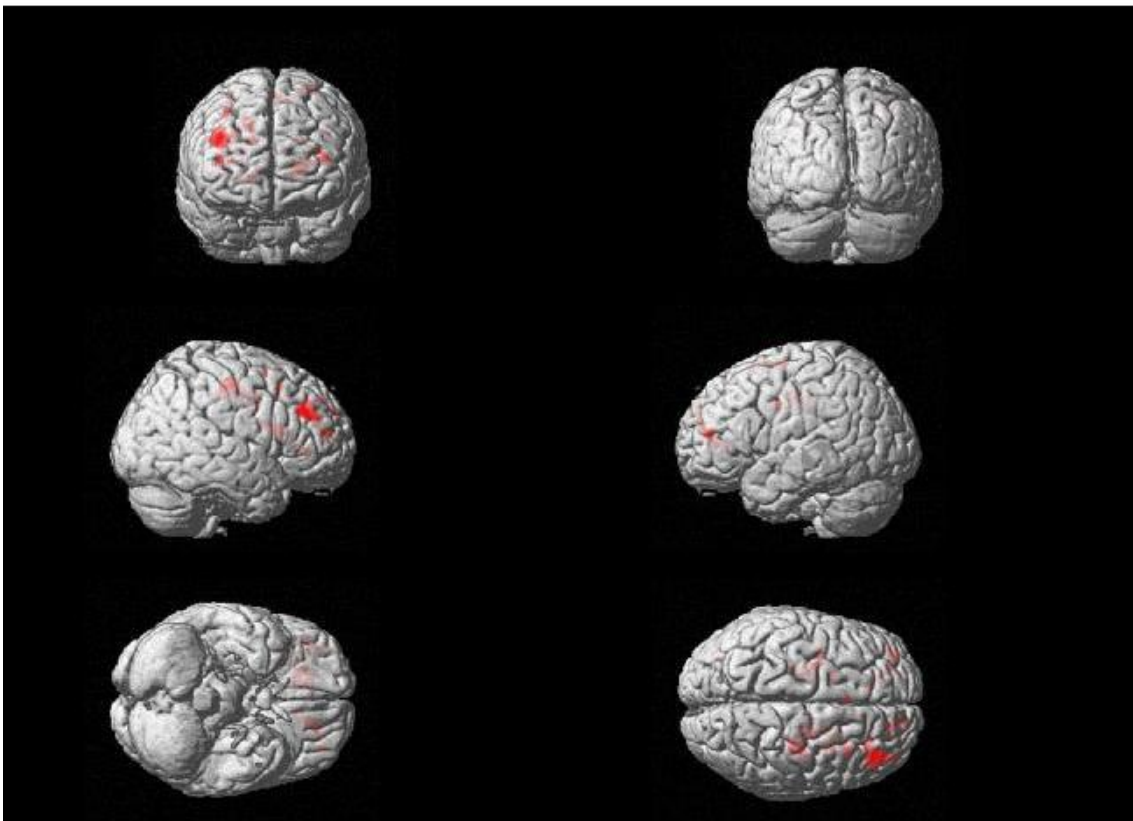


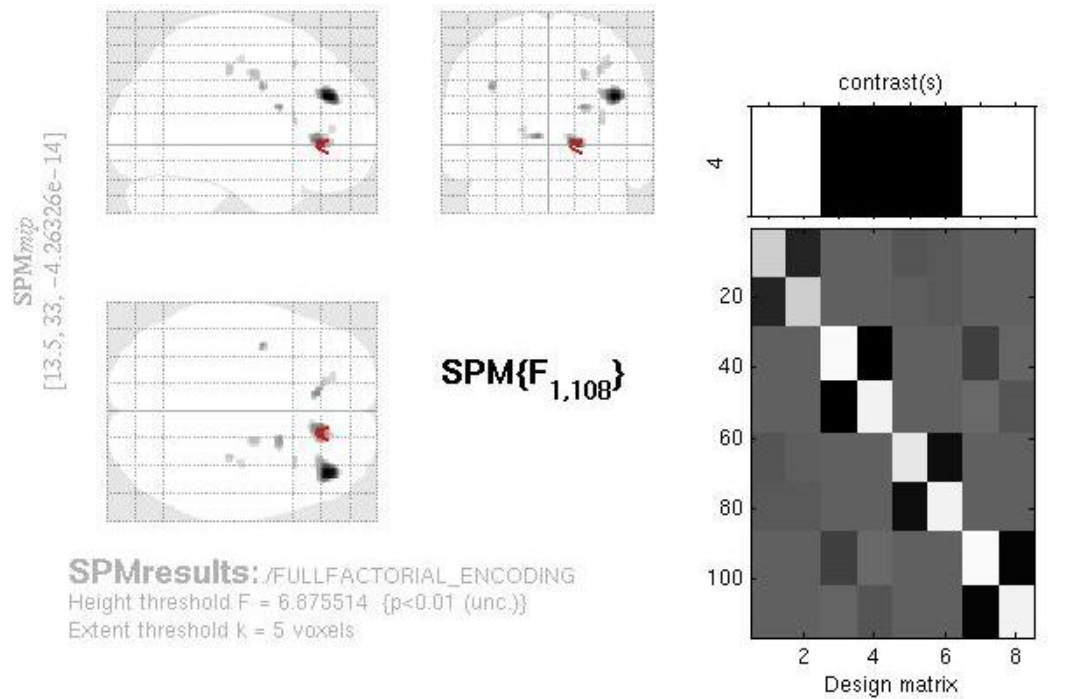
Figure 6-32: T contrast of time x group at $p < 0.01$ uncorrected, rendered on single participant template from SPM8.

Several predominantly frontal regions reached this liberal significance level. (Table 6-16, Figure 6-32 and Figure 6-33).

value	P (uncorr)	COORDINATES x, y, z	AREA
10.14	0.002	40, 39, 28	RDLPFC
8.96	0.003	14, 33, 0	RIGHT CORPUS CALLOSUM
8.1	0.005	-8, 32, 3	LEFT FRONTAL
7.19	0.008	-15, 36, 3	LEFT FRONTAL
7.93	0.006	21, 8, 21	RIGHT SUB CORTICAL
7.89	0.006	-38, -3, 34	LEFT INF FRONTAL
7.36	0.008	21, -9, 42	RIGHT FRONTAL SUB GYRAL

Table 6-16: Whole brain analysis of time x group F contrast
Coordinates of voxel clusters $k > 20$, with a significance level of < 0.01 uncorrected are shown.

T contrasts revealed that the direction of the significant effects was in the same as in the defined ROIs, with a reduction in activation in the training group as a result of training (Figure 6-34 and Figure 6-35).



Statistics: *p*-values adjusted for search volume

set-level	cluster-level				peak-level						mm mm mm		
	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>k</i> _E	<i>p</i> _{uncorr}	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>F</i>	(<i>Z</i> _z)	<i>p</i> _{uncorr}				
11			249		0.936	0.991	10.14	2.89	0.002		40	39	28
			89		0.985	0.991	8.96	2.71	0.003		14	33	-0
			18		0.997	0.991	8.10	2.56	0.005		-8	32	3
					1.000	0.991	7.19	2.39	0.008		-15	36	3
			29		0.998	0.991	7.93	2.53	0.006		21	8	21
			23		0.998	0.991	7.89	2.52	0.006		-38	-3	34
			24		0.999	0.991	7.36	2.42	0.008		21	-9	42

Figure 6-33: SPM for Time x group interaction (F contrast)
Clusters of > 20 voxels at p < 0.01 (uncorrected) are shown.

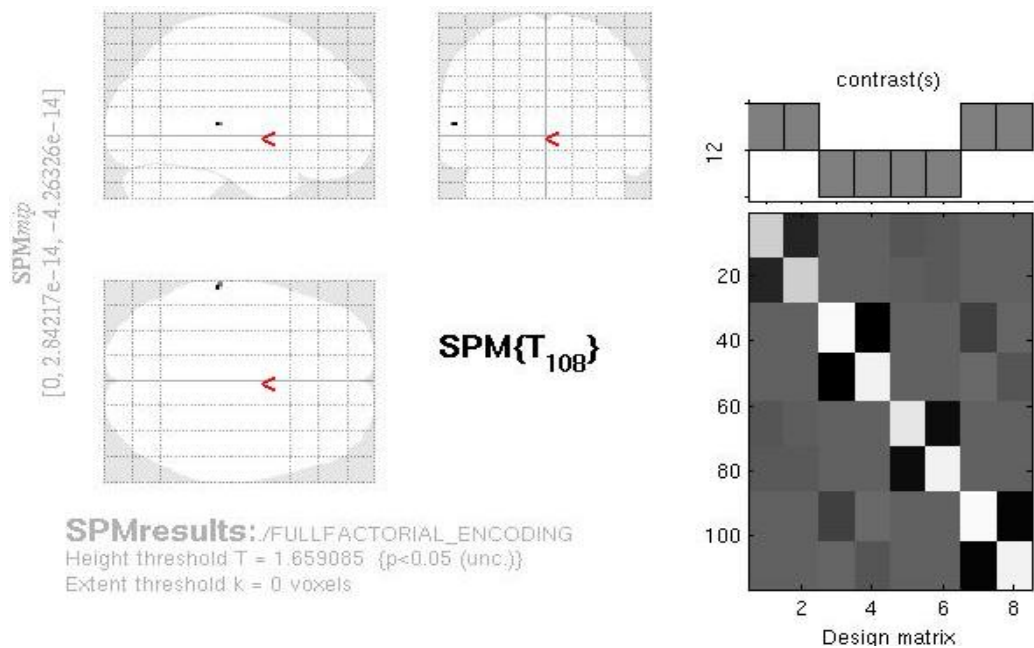


Figure 6-34: SPM of whole brain analysis, positive time x group T contrast

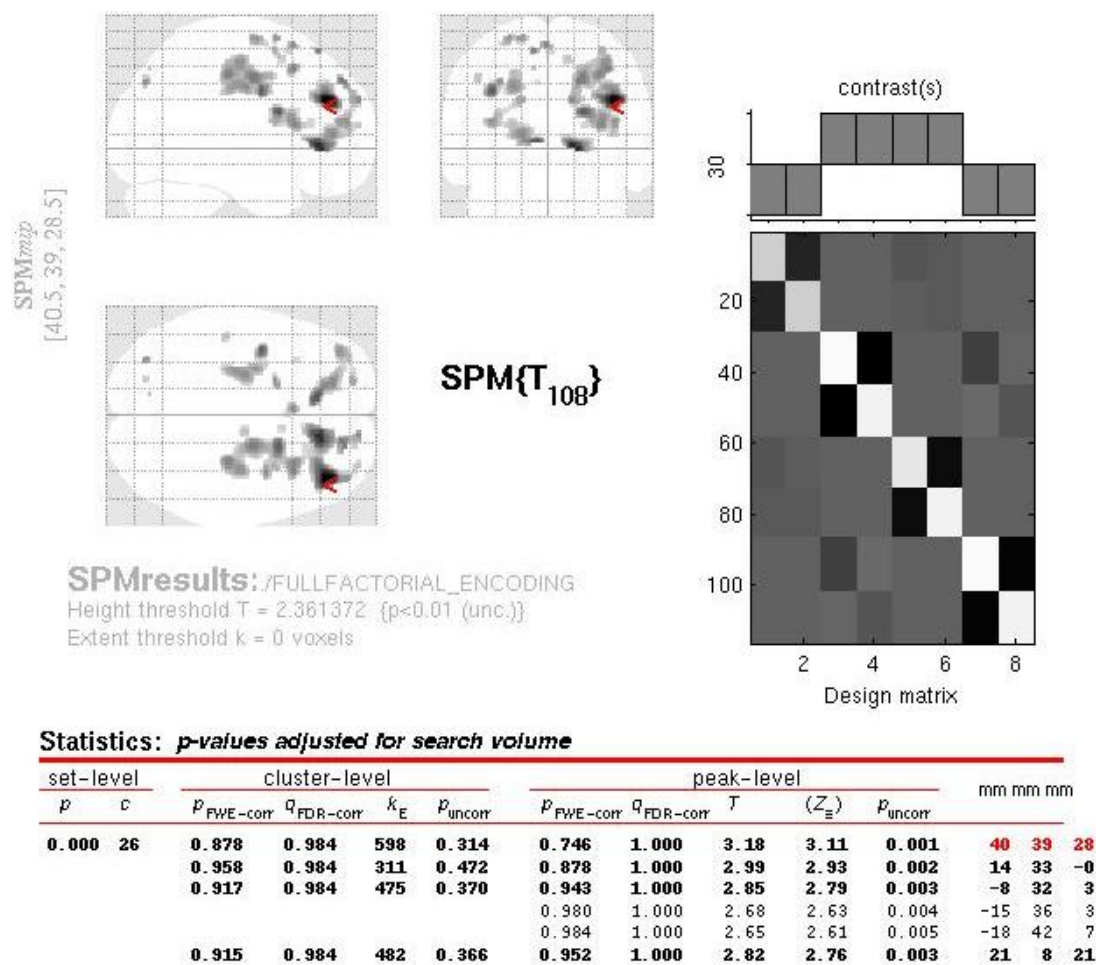


Figure 6-35 SPM of whole brain analysis (negative time x group T contrast, $p < 0.01$ (uncorrected))

6.7.1 EFFECTS OF TRAINING - TIME X TRIAL TYPE X GROUP CONTRASTS

Whole brain analysis examining the F contrast for time x trial type x group revealed a number of frontal, parietal and subcortical areas that reached significance at the liberal uncorrected threshold of $p < 0.01$. At the cluster level, a right subcortical area at $x = 21$, $y = -7$, $z = 3$, reached significance at $p_{FWE} < 0.05$. T contrasts revealed that the coordinates reaching significance were for the negative interaction (see Table 6-17, Figure 6-36, Figure 6-37, Figure 6-38, and Figure 6-39).

F	k_E	COORDINATES	AREA
		x, y, z	
13.54	2732	21, -7, 3	Thalamus / globus pallidus

Table 6-17: Whole brain analysis of time x trial x group contrast
Coordinates of cluster significant at cluster-level $p_{FWE} < 0.05$ shown

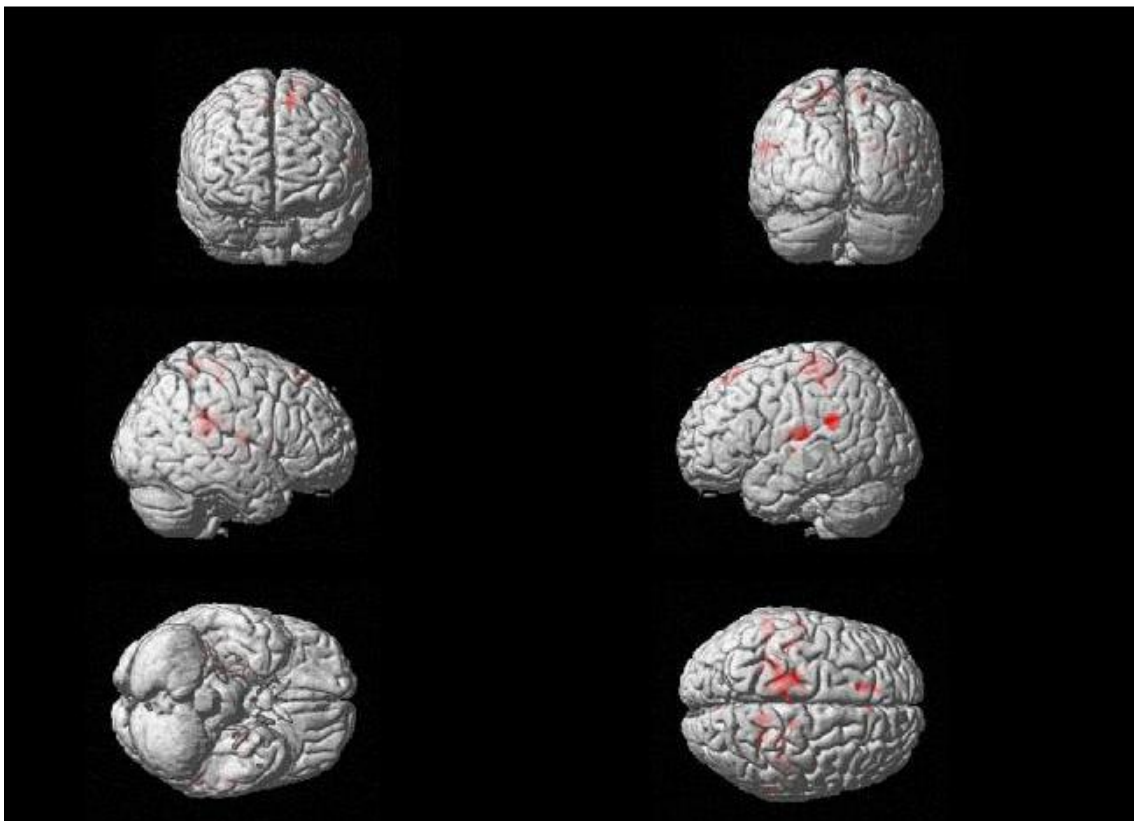
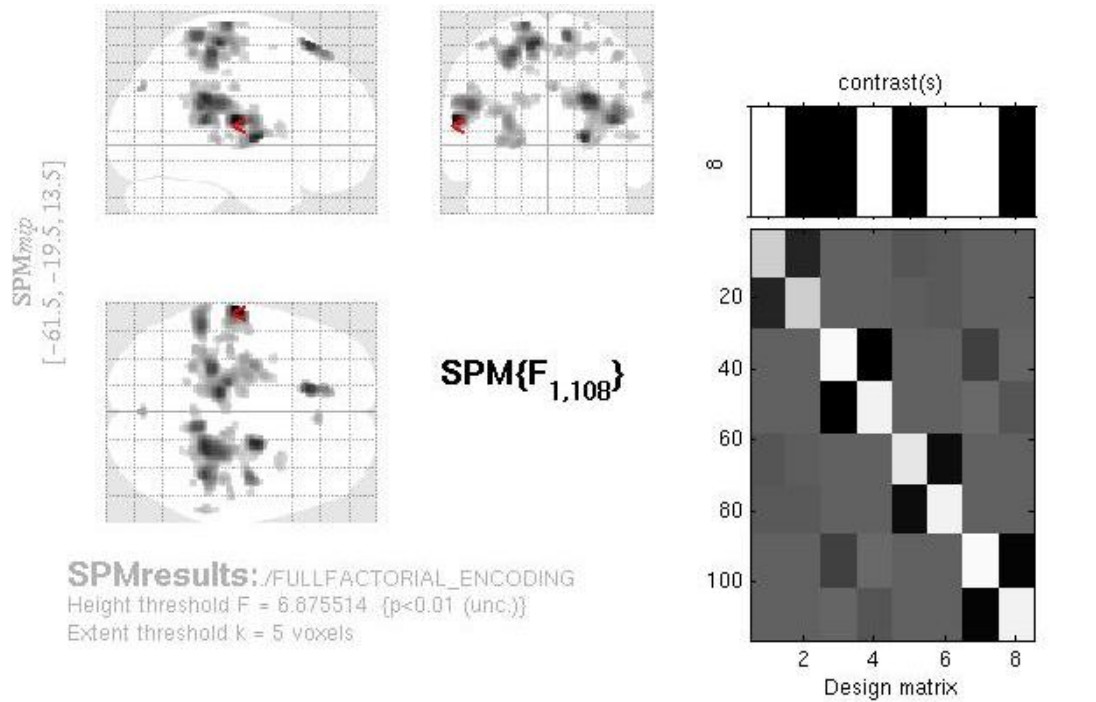


Figure 6-36: Time x trial x group F contrast at $p < 0.01$, rendered on a single participant template from SPM8



Statistics: *p-values adjusted for search volume*

set-level	cluster-level				peak-level					mm mm mm		
	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>k</i> _E	<i>p</i> _{uncorr}	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>F</i>	(<i>Z</i> _≡)	<i>p</i> _{uncorr}			
32			417		0.340	0.983	15.19	3.58	0.000	-62	-19	13
			2732		0.539	0.983	13.54	3.38	0.000	21	-7	3
					0.566	0.983	13.34	3.35	0.000	22	-39	27
					0.683	0.983	12.49	3.24	0.001	40	-39	13
			1668		0.591	0.983	13.15	3.33	0.000	-10	-30	61

Figure 6-37: SPM of whole brain analysis, F contrast of time x trial type x group, $p < 0.01$ (uncorrected)

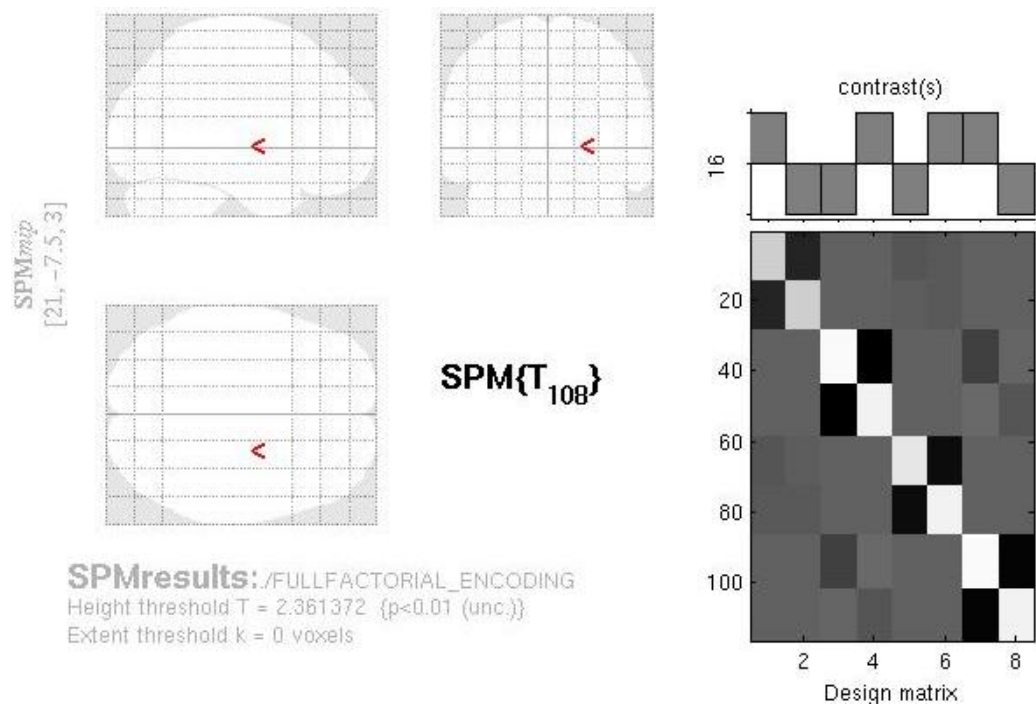
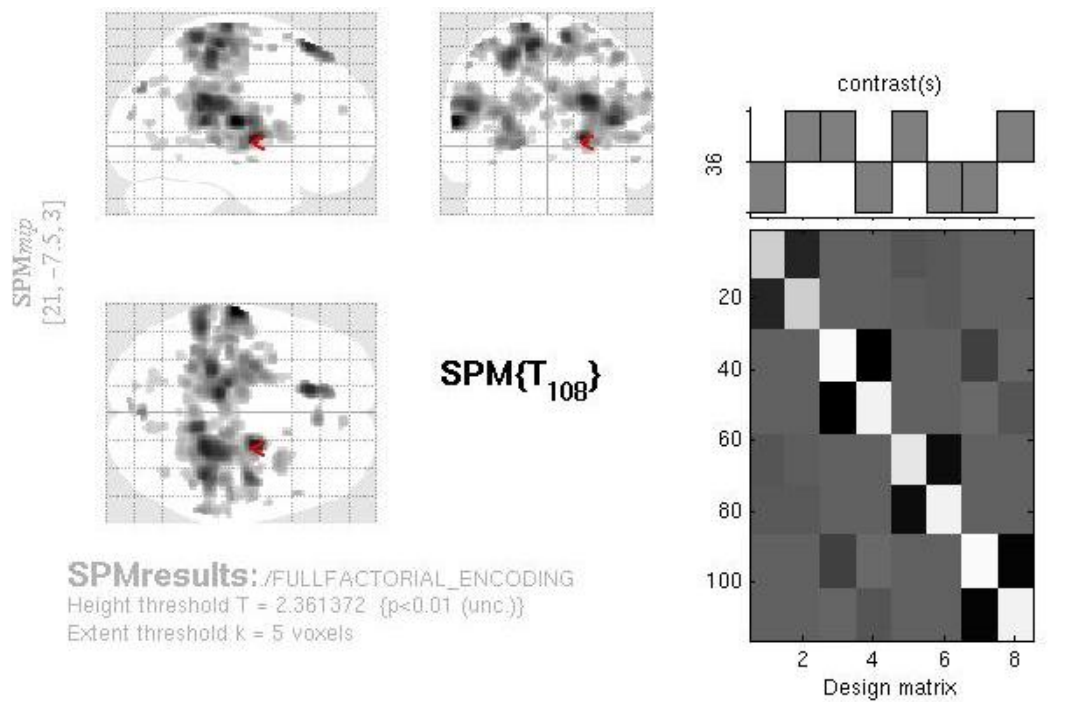


Figure 6-38: SPM of whole brain analysis with time x trial x group T contrast, $p < 0.01$ (uncorrected)



Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level					mm mm mm		
p	C	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_{eq})	p_{uncorr}			
0.000	45	0.283	0.984	2498	0.049	0.188	0.999	3.90	3.76	0.000	-62	-19	13
						0.743	0.999	3.19	3.11	0.001	-27	-7	12
						0.829	0.999	3.07	3.00	0.001	-20	-12	-0
		0.026	0.245	6264	0.004	0.321	0.999	3.68	3.56	0.000	21	-7	3
						0.341	0.999	3.65	3.54	0.000	22	-39	27
						0.437	0.999	3.53	3.43	0.000	40	-39	13
		0.075	0.366	4505	0.012	0.361	0.999	3.63	3.51	0.000	-10	-30	61
						0.449	0.999	3.52	3.42	0.000	-24	-34	54
						0.511	0.999	3.45	3.35	0.000	-16	-25	72

Figure 6-39: SPM of whole brain analysis with negative time x trial x group T contrast, $p < 0.01$ (uncorrected)

6.8 EXPLORATORY SUBCORTICAL ANALYSIS

As the T contrast had revealed a sub cortical area that reached significance at the cluster level, further exploratory analysis was conducted. Previous studies have demonstrated that successful cognitive training is associated with increased activation in striatal areas ¹⁷⁷. Dahlin et al demonstrated that in older healthy participants, successful WM training was associated with increased activation in a left striatal area, with peak activation at $x = -24, y = 10$, and $z = -2$)¹⁷⁷. Exploratory analysis was therefore conducted at 10mm spheres around the central coordinates of the significant cluster identified from the current study and from the Dahlin et al study to examine whether there was evidence for a training related increase in subcortical activation. (Figure 6-40).

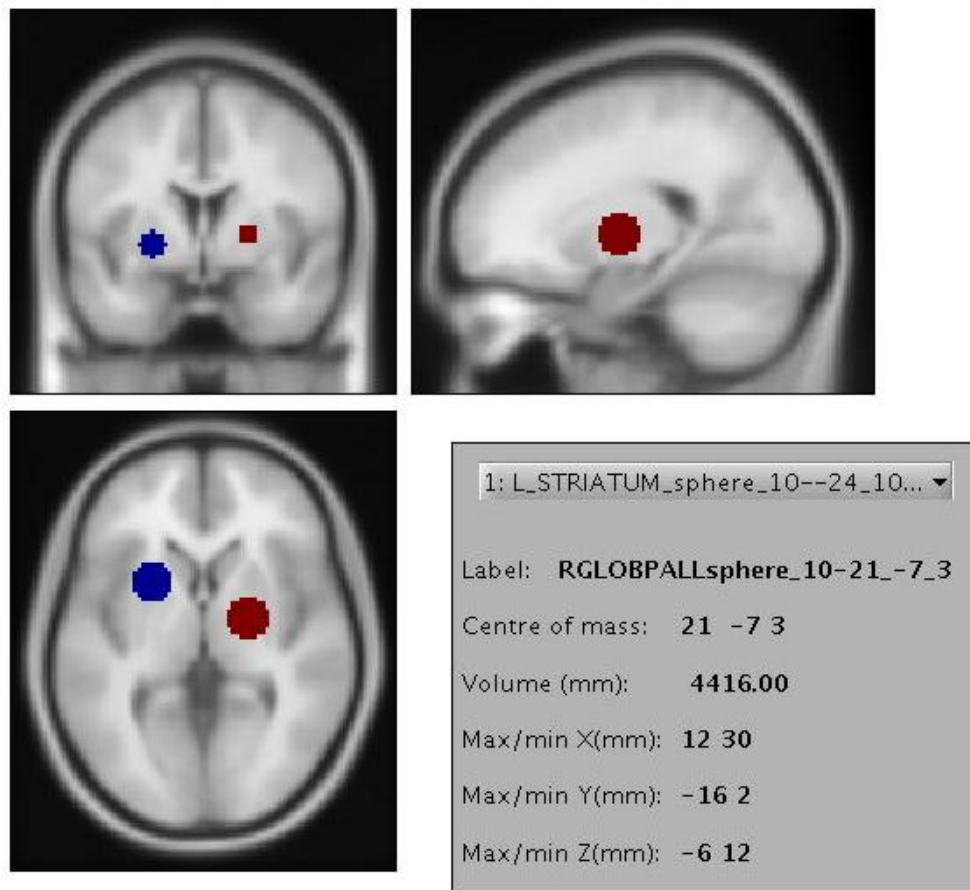


Figure 6-40: Striatal ROI defined from whole brain analysis and Dahlin et al¹⁷⁷.

MarsBar was used to estimate β values for the subcortical ROI as above, and the values were then entered into a repeated measures ANOVA to examine for significant effects and interactions.

The training group showed increased activation for random trials, but reduced activation for structured trials, whilst the control group demonstrated increased activation for both trial types (Table 6-18, Figure 6-41, Figure 6-42).

	L STRIATUM F (p)	R STRIATUM F (p)
MAIN EFFECTS		
TIME	1.184 (0.286)	0.579 (0.453)
TRIAL	1.491 (0.233)	6.627 (0.016)
BETWEEN GROUP	0.012 (0.912)	0.067 (0.798)
INTERACTIONS		
TIME x GROUP	1.496 (0.232)	0.748 (0.395)
TRIAL x GROUP	0.061 (0.807)	0.196 (0.662)
TIME x TRIAL	0.012 (0.915)	2.135 (0.156)
TIME x TRIAL x GROUP	3.918 (0.058)	8.728 (0.006)

Table 6-18: ANOVA results for the striatal ROIs

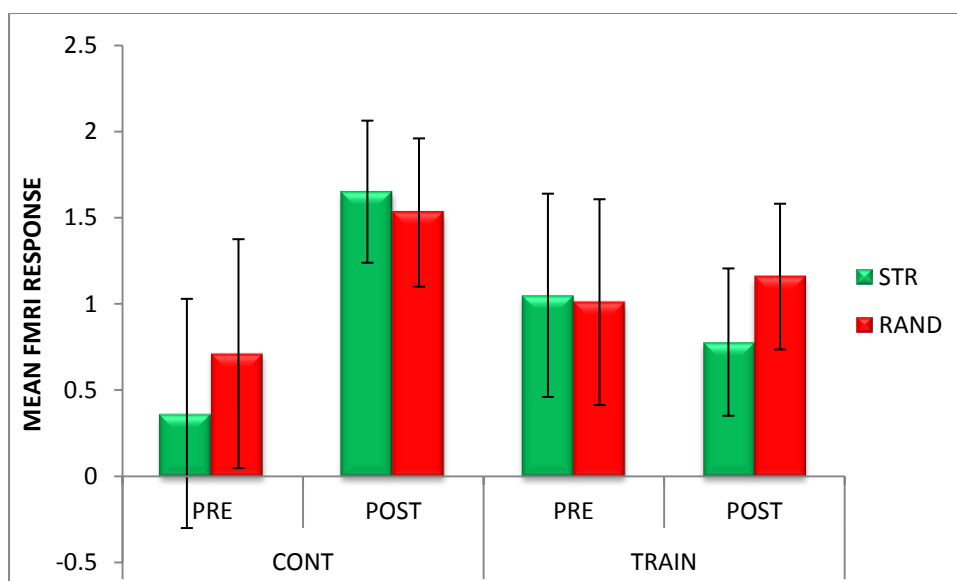


Figure 6-41: L STRIATUM: Mean fMRI response for both groups and time points
Error bars are SEM. Time x trial x group interaction approaches significance ($p = 0.058$)

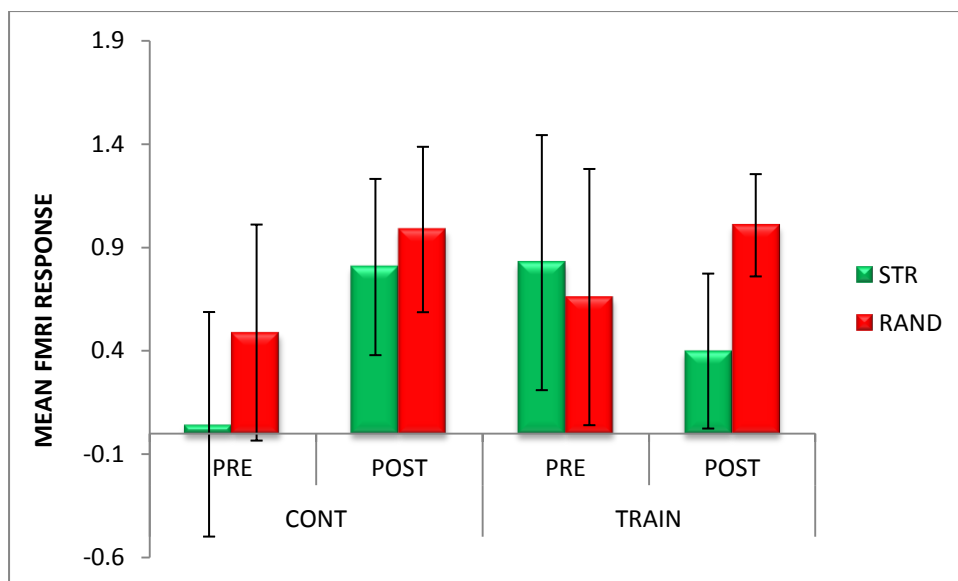


Figure 6-42: Mean fMRI response for Right Striatal ROI
 Error bars are SEM. Time x trial x group interaction is significant ($p = 0.006$).

6.9 WHOLE BRAIN ANALYSIS - EFFECT OF CHUNKING

The whole brain main effect of chunking was also examined with the F and T contrasts of the main effect of trial type. As shown in Figure 6-44, Figure 6-45, and Figure 6-46, a number of predominantly parietal and occipital voxels reached significance at the liberal threshold of $p < 0.01$ uncorrected. Table 6-19 shows voxel clusters that reached significance at $p_{FWE} < 0.05$. These were in the parietal lobe (BA40) and occipital lobe. Of note, the significant contrast was the random > structured; participants demonstrating increased activation during random compared to structured trials.

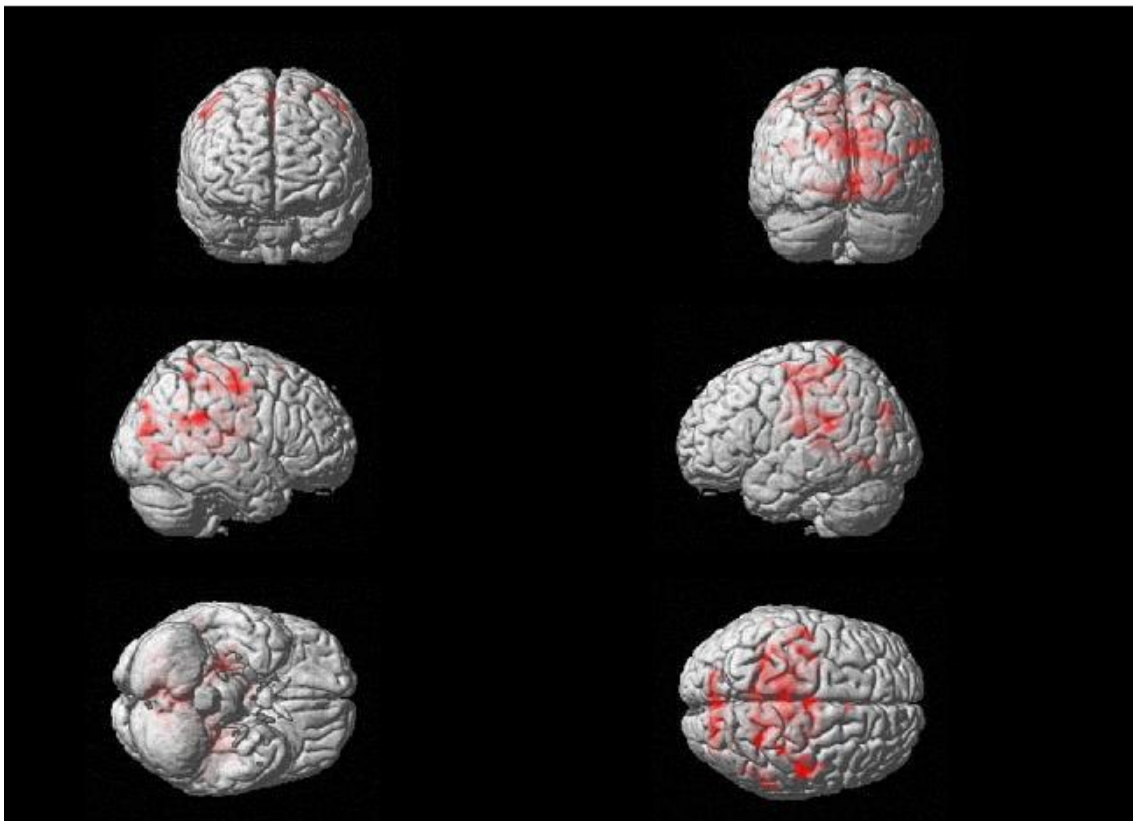
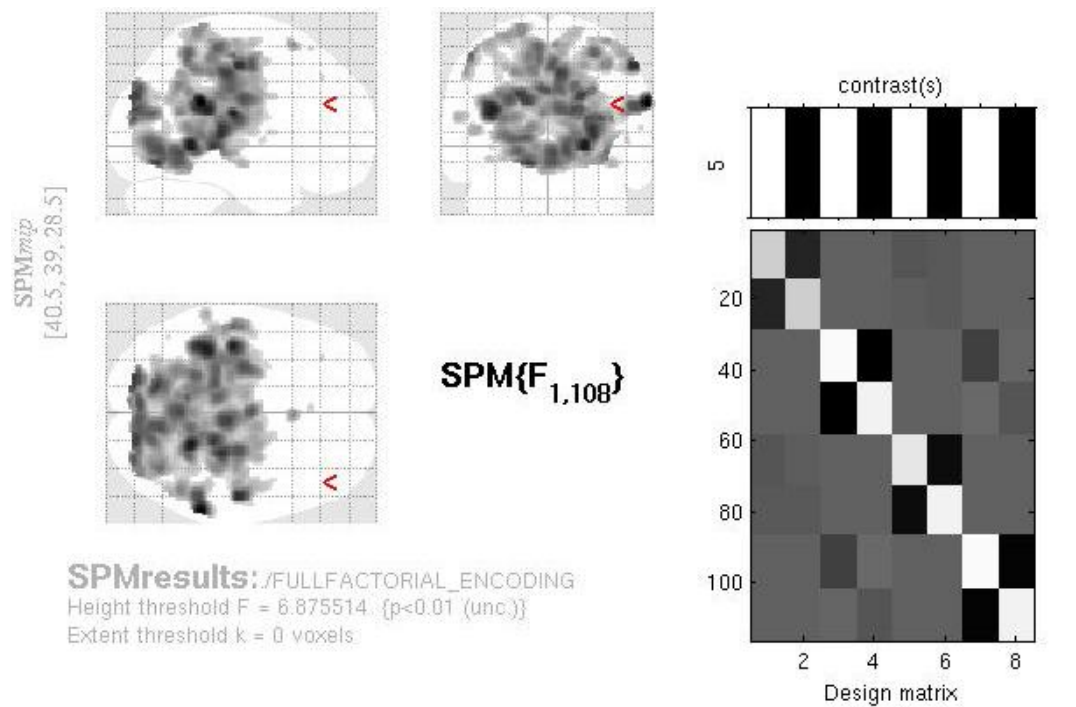


Figure 6-43: Main effect of trial type F contrast at $p < 0.01$ rendered on single participant template in SPM8

k_E	F value	Coordinates	AREA
		x, y, z	
1048	17.86	62, -42, 25	BA40- PARIETAL
33357	16.46	21, -48, -2	OCCIPITAL

Table 6-19: Whole brain analysis of Main effect of trial type
Significant cluster coordinates shown.



Statistics: *p-values adjusted for search volume*

set-level		cluster-level				peak-level					mm mm mm		
<i>p</i>	<i>c</i>	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>k</i> _E	<i>p</i> _{uncorr}	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>F</i>	<i>(Z_z)</i>	<i>p</i> _{uncorr}			
0.000	21			1048		0.141	0.486	17.86	3.89	0.000	62	-42	25
						0.512	0.486	13.74	3.40	0.000	54	-43	22
						0.848	0.525	11.16	3.05	0.001	49	-55	19
				33357		0.227	0.486	16.46	3.73	0.000	21	-48	-2
						0.266	0.486	15.98	3.68	0.000	-38	-39	21
						0.268	0.486	15.96	3.68	0.000	-39	-21	18
				750		0.330	0.486	15.29	3.60	0.000	52	-18	48

Figure 6-44: SPM of main effect of trial type F contrast during encoding
 Voxels significant at $p < 0.001$ (uncorrected) are shown.

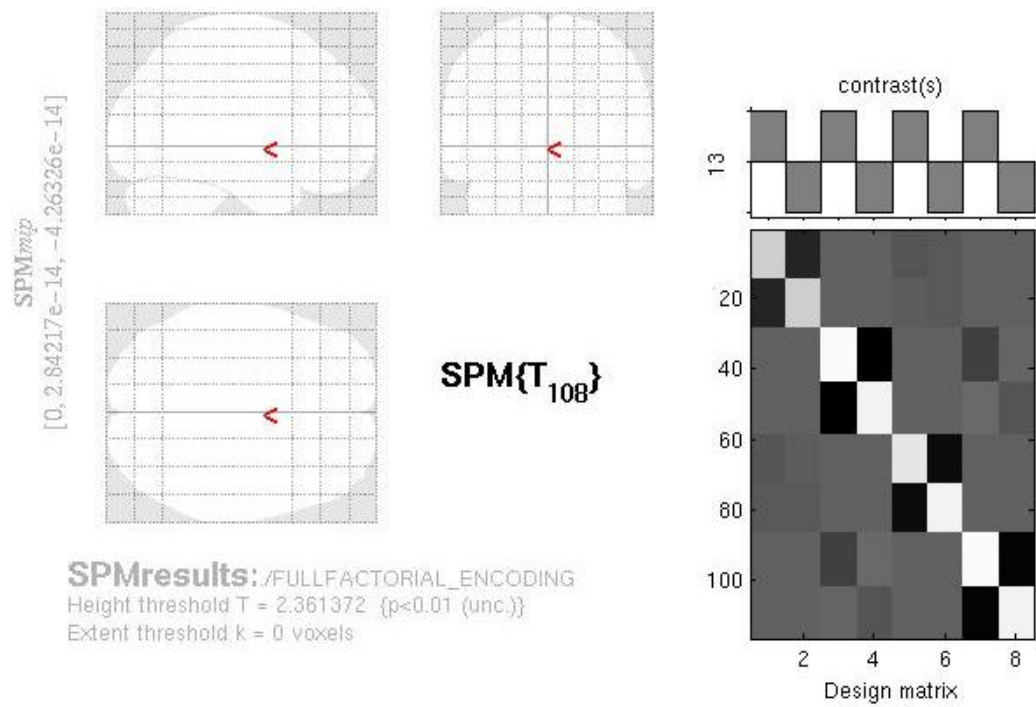
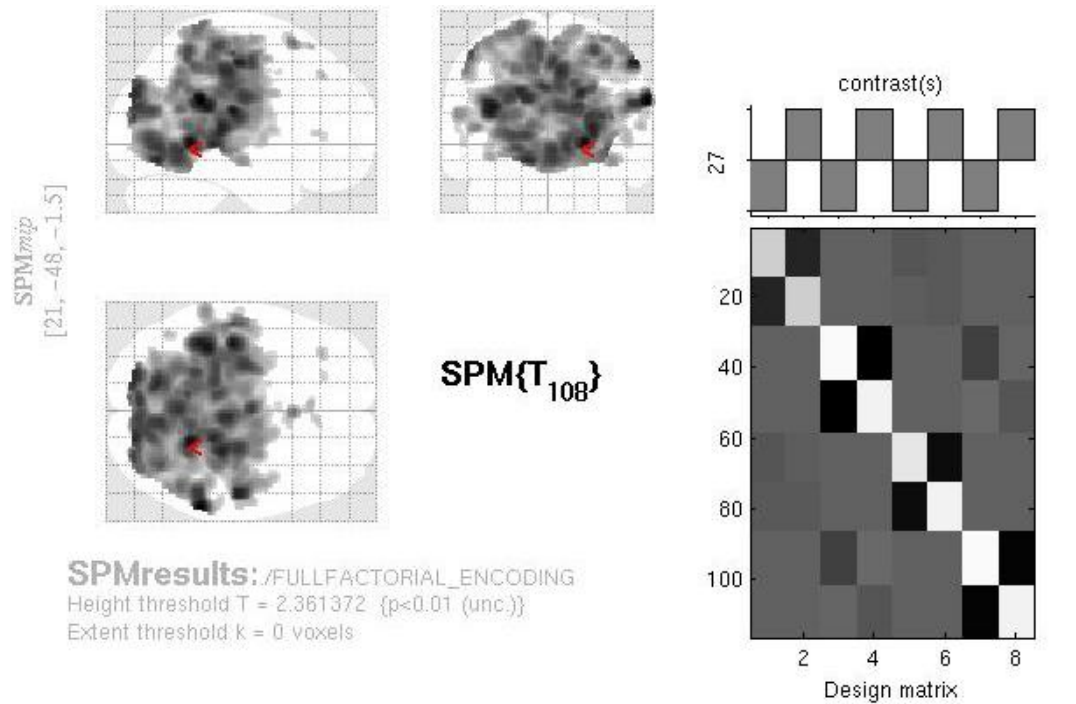


Figure 6-45: SPM of Structured > Random trial T contrast across both groups and time points during encoding



Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level					mm mm mm		
p	C	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_{π})	p_{uncorr}			
0.000	18	0.000	0.000	61017	0.000	0.073	0.372	4.23	4.06	0.000	62	-42	25
						0.121	0.372	4.06	3.91	0.000	21	-48	-2
						0.143	0.372	4.00	3.85	0.000	-38	-39	21

Figure 6-46: SPM of Random > structured T contrast across both groups and time points during encoding
The significant cluster $p_{FWE} < 0.001$ is shown

6.10 DELAY ANALYSIS

6.10.1 EFFECT OF TRAINING ON ROIs

The delay period of interest is the variable time point during which participants were asked to hold the 5 digits they had just seen in working memory, prior to the cue to recall the digit span. The same 4 main ROIs were examined as had been during the encoding phase.

A repeated measures ANOVA with time, trial type, ROI and hemisphere as within participants factors and group as the between participants factor revealed a near significant main effect of trial type ($F(1,27) = 3.950, p = 0.057$) and a significant main effect of ROI ($F(1,27) = 9.395, p = 0.005$).

There were no other significant main effects or interactions (see Table 6-20).

MAIN EFFECTS	F	Sig.(p)
TIME	0.094	0.761
TRIAL	3.950	0.057
ROI	9.395	0.005
INTERACTIONS		
TIME x GROUP	1.245	0.274
TRIAL x GROUP	0.584	0.451
ROI x GROUP	0.123	0.729
TIME x TRIAL x GROUP	0.584	0.451
TIME x TRIAL x ROI x GROUP	0.199	0.659

Table 6-20: ANOVA results for the delay event.

Therefore, although there were no significant effects of training, it is notable that the pattern of activation change from the encoding phase persisted during the delay phase - with training leading to a reduction in activation (mean = -0.60 (SD = 2.82)) compared to an increase in controls (mean = 1.06 (SD = 4.96)). However due to the large variance this group difference was not significant ($t(28) = 1.116, p = 0.274$), (see Figure 6-47).

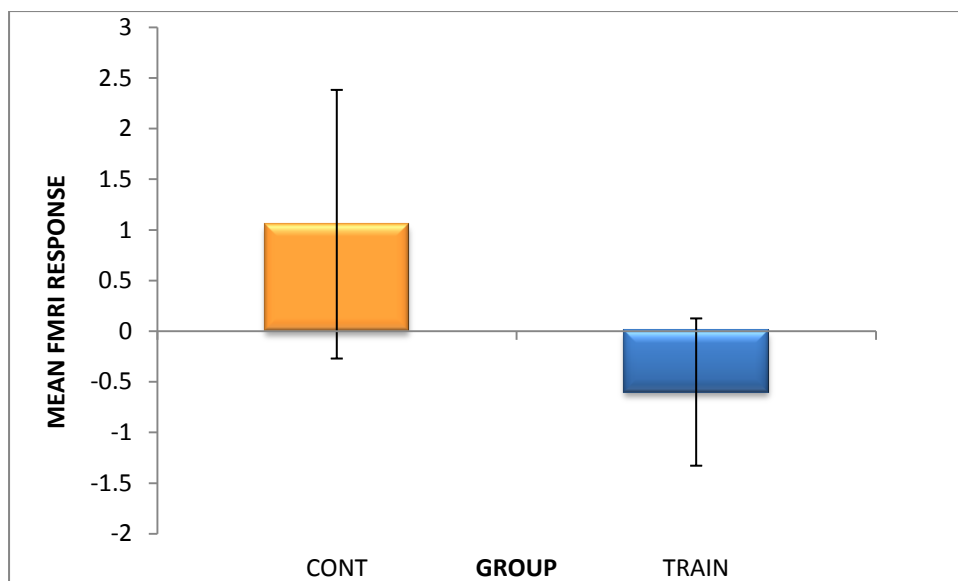


Figure 6-47: Mean change in fMRI response across all 4 ROIs and trial types. Error bars are SEM.

6.10.2 EFFECT OF CHUNKING

The main effect of trial type approached significance ($p = 0.057$). There was a positive effect of chunking at both time points and for both groups with increased activation across all 4 ROIs for structured compared to random trials. Of note, this reduced in the training group but increased in the control group following intervention; however these interactions were not significant (Figure 6-48).

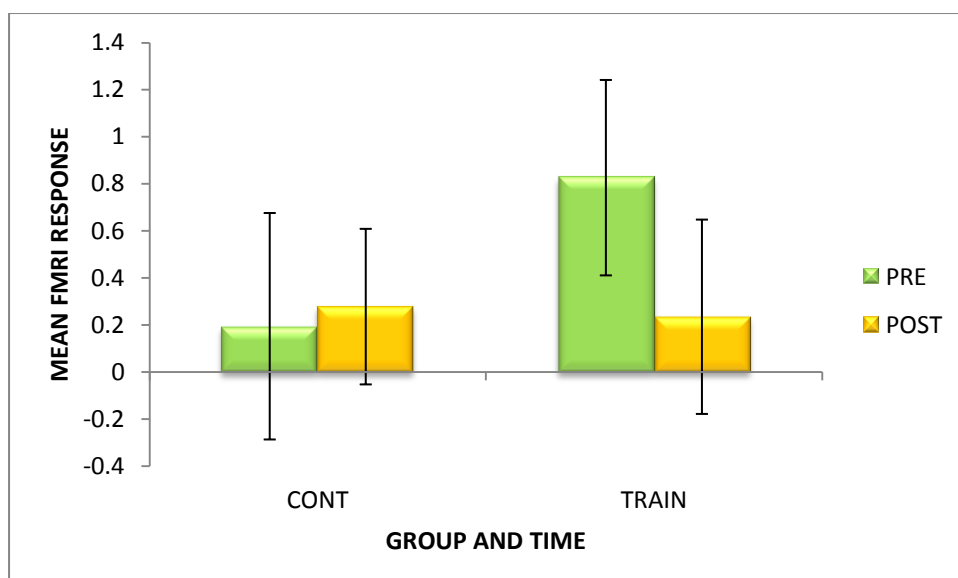


Figure 6-48: Mean fMRI response with chunking contrast (structured trials values – random trials values). Error bars are SEM.

6.10.3 DELAY ANALYSIS - WHOLE BRAIN

Results of whole brain analysis were also examined to identify any additional significant regions, other than the defined ROIs.

6.10.3.1 EFFECTS OF TRAINING ON WHOLE BRAIN DURING DELAY

The time by group F and T contrasts was examined for the whole brain, with a liberal threshold of $p = 0.01$ uncorrected. As shown in Figure 6-50, Figure 6-51 and Figure 6-52, there were occipital, parietal and temporal voxels that were significant at $p < 0.01$ uncorrected. One occipital cluster (at $x = 6, y = -84, z = 19$) reached significance at $p_{FWE} < 0.05$.

As shown in Figure 6-53, the time \times trial type \times group F contrast revealed only a small number of widely distributed voxels that reached significance at $p < 0.01$ uncorrected.

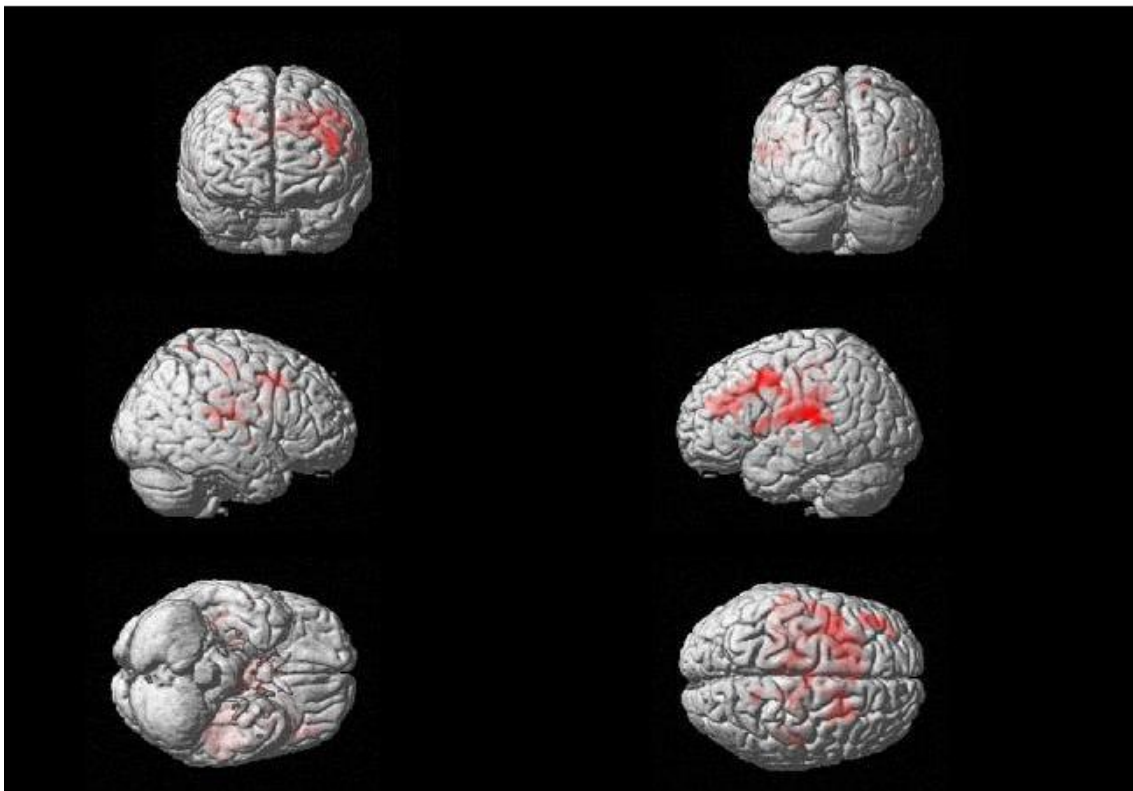
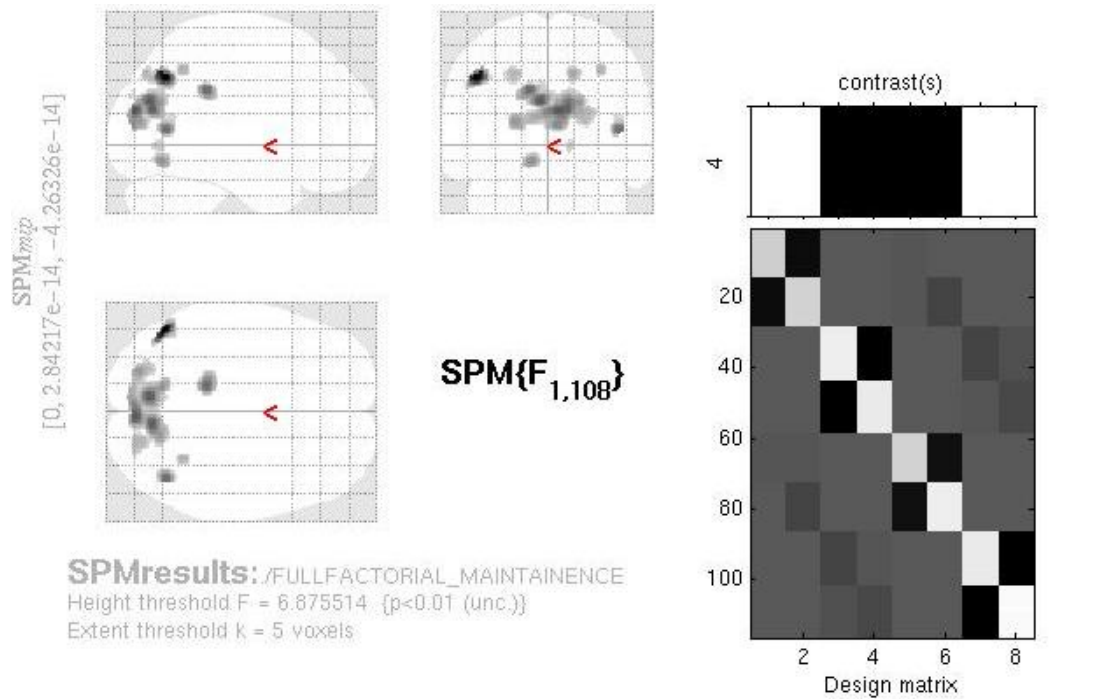


Figure 6-49: T contrast of Structured > Random trials
 $p < 0.01$ (uncorrected), rendered on a single participant template in SPM8.



Statistics: p -values adjusted for search volume

set-level	cluster-level				peak-level					mm mm mm		
	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	F	(Z_{Ξ})	p_{uncorr}			
11			136		0.562	0.958	13.31	3.35	0.000	-48	-64	40
					1.000	0.958	7.12	2.38	0.009	-54	-61	33
					0.894	0.958	10.63	2.97	0.001	6	-84	19

Figure 6-50: SPM of time x group F contrast for delay
 $p < 0.01$ (uncorrected). Coordinates of largest clusters of significant voxels are shown.

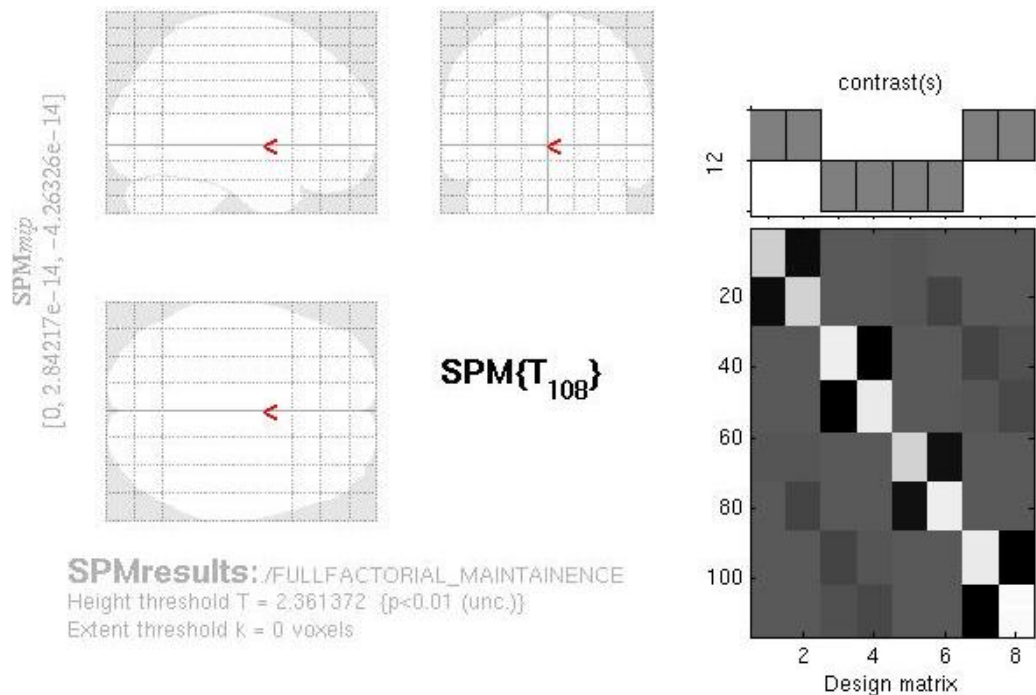


Figure 6-51: SPM of positive group x time interaction T contrast during delay
There are no significant voxels at $p < 0.01$ (uncorrected).

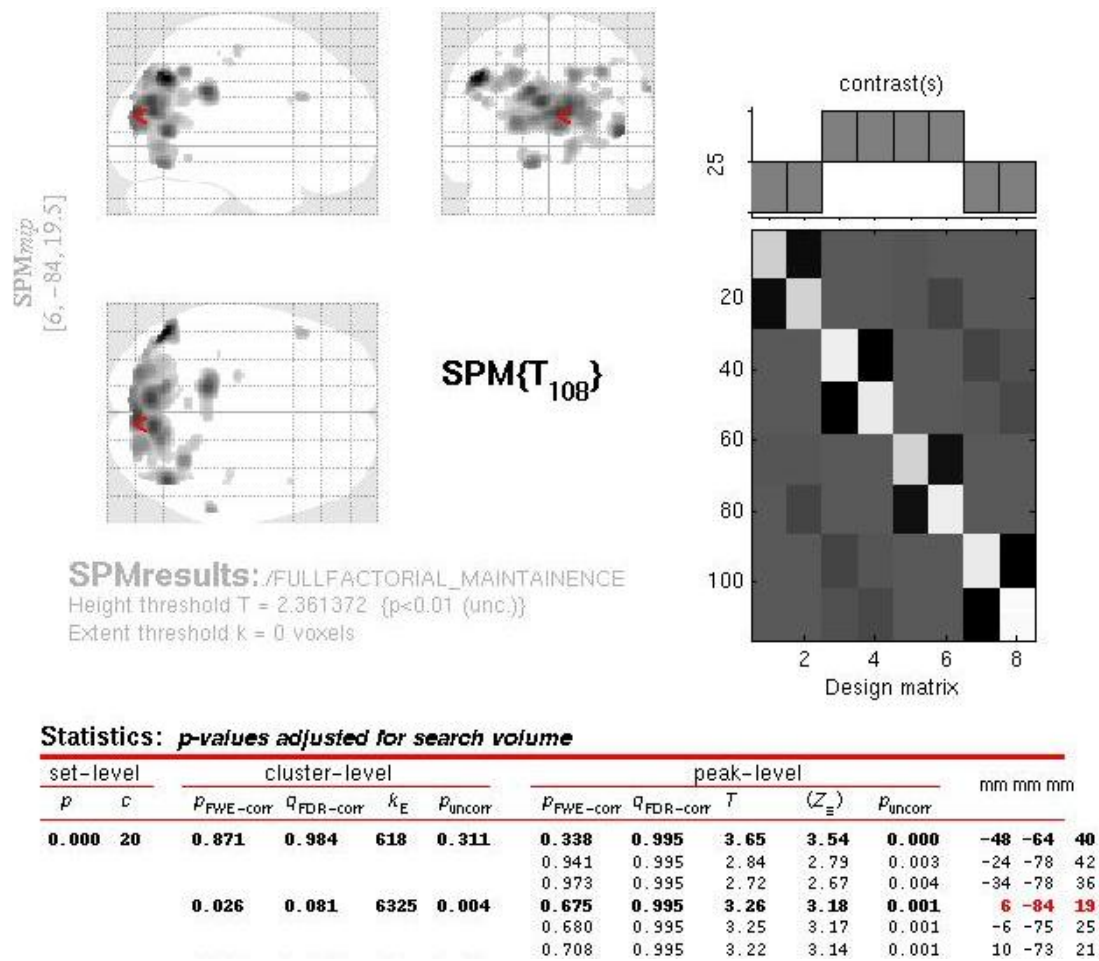


Figure 6-52: SPM of negative time x group T contrast during delay
Significant cluster voxels $p_{FWE} < 0.05$ are shown.

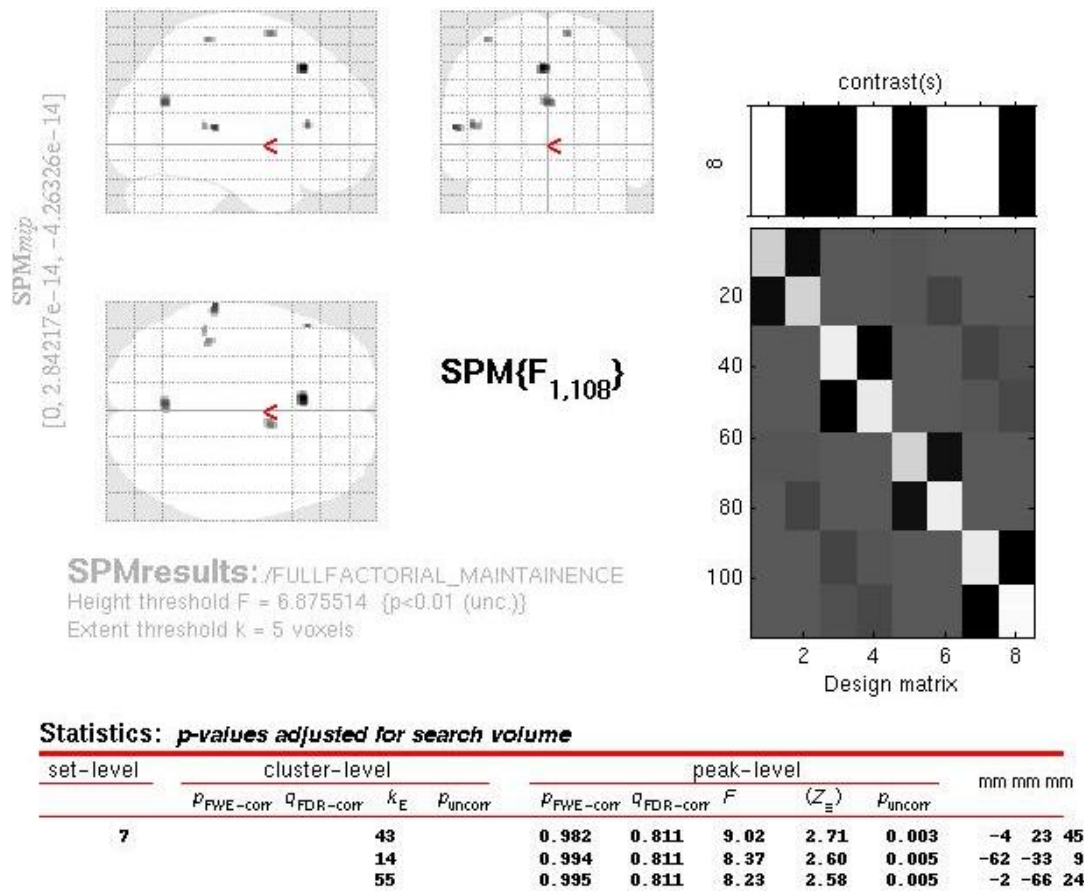


Figure 6-53: SPM of time x trial type x group F contrast for delay
Only voxels significant at $p < 0.005$ (uncorrected) are shown.

6.10.3.2 EFFECT OF CHUNKING ON WHOLE BRAIN DURING DELAY

The effects of chunking were examined with the F and T contrasts for main effect of trial.

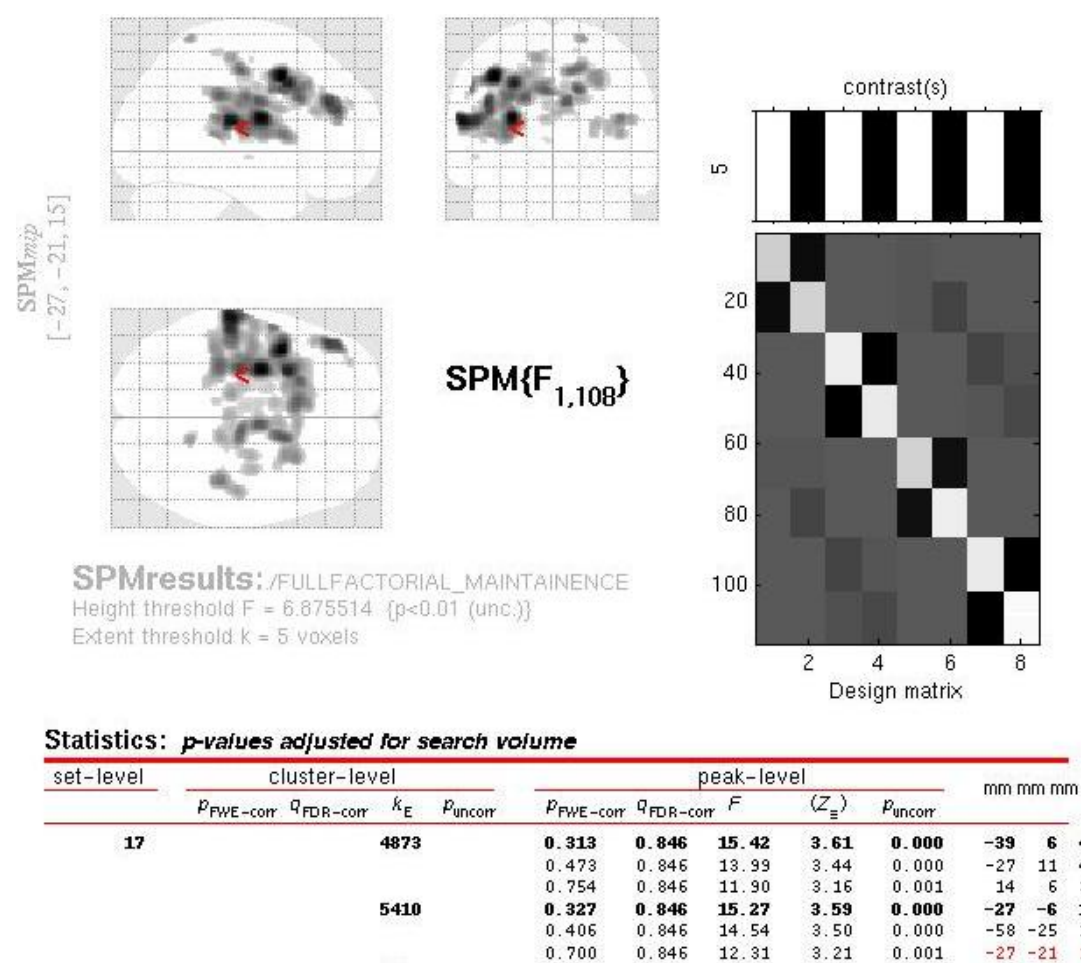


Figure 6-54: SPM of main effect of trial type (F contrast) during delay
Only voxels significant at $p = 0.001$ (uncorrected) are shown.

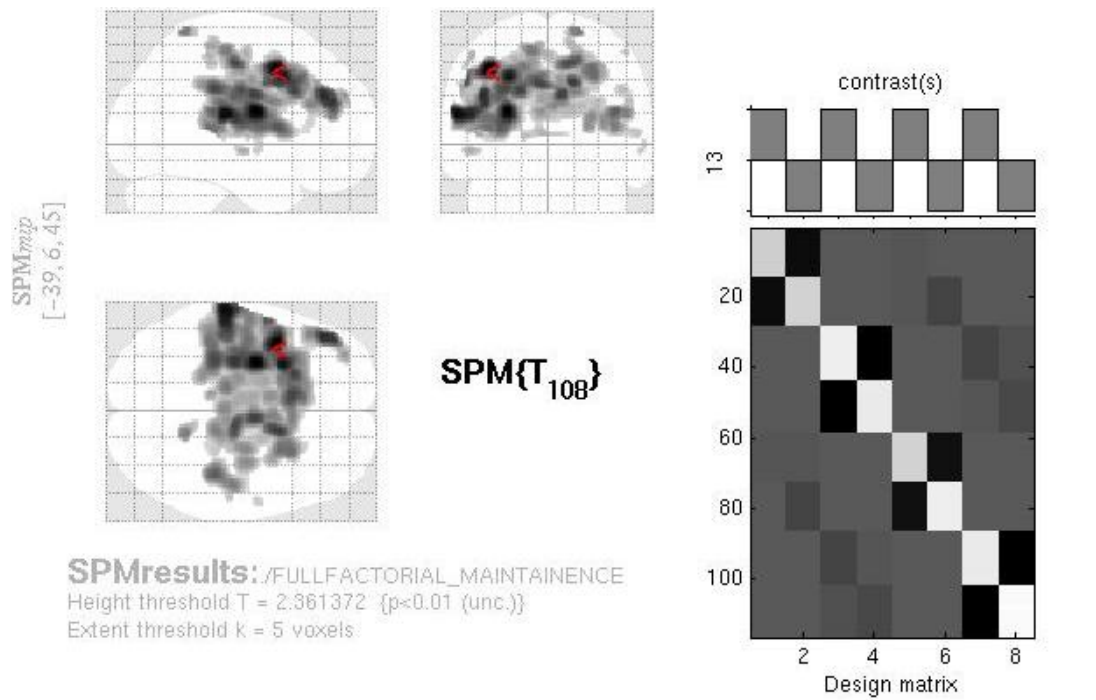


Figure 6-55: SPM of structured > random T contrast across both groups and time points during delay
Voxels significant at the cluster level $p_{FWE} < 0.05$ are shown.

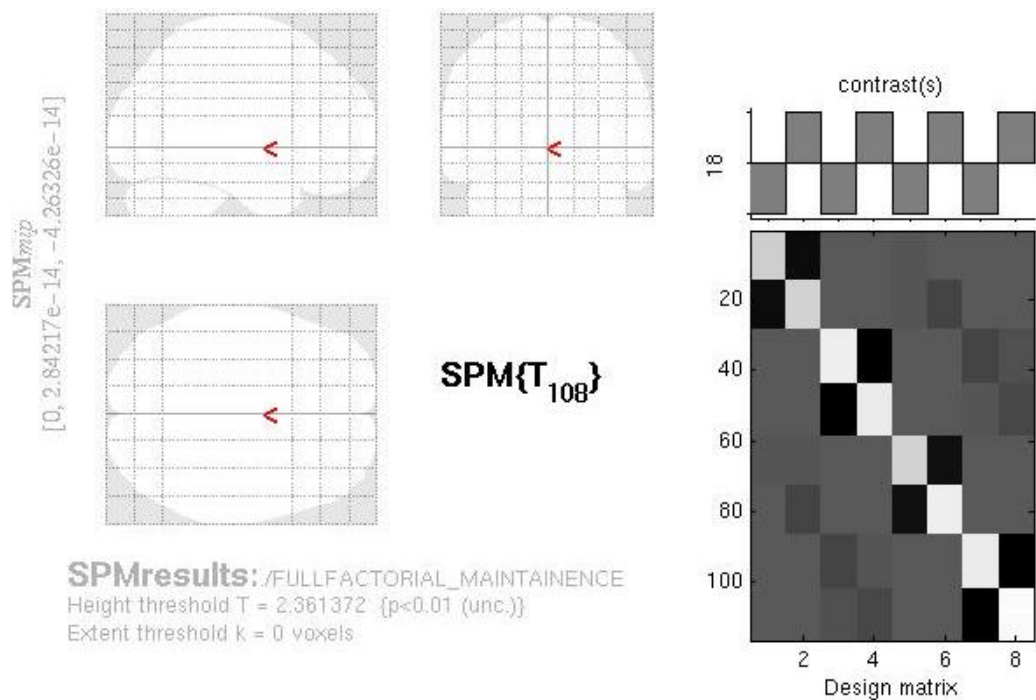


Figure 6-56: SPM of random > structured contrast across both groups and time points for delay
There are no significant voxels at $p < 0.01$ (uncorrected).

As can be seen in Figure 6-49, Figure 6-54, Figure 6-55 and Figure 6-56, a range of frontal, temporal and parietal voxels reached significance at $p < 0.01$ uncorrected. For the structured > random T contrasts across all groups and time points, there was a significant frontal cluster (cluster level $p_{FWE} < 0.001$). (Table 6-21).

K_E	T	COORDINATES x, y, z	REGION
25438	3.93	-39, 6, 45	FRONTAL LOBE

Table 6-21: Whole brain analysis of structured > random t contrast during delay phase
Coordinates of largest clusters of significant voxels shown. (cluster significant at $p_{FWE} < 0.001$).

Therefore, the effect of trial type appeared to differ between the encoding and delay phases, with random trials producing greater activation than structured trials during encoding, but the reverse pattern emerging during the delay phase.

6.11 ANALYSIS OF RECALL PHASE

As verbal responses were given during the recall phase, movement artefact due to speech prevented meaningful analysis of this event. Therefore the recall events were modelled as regressors of no interest and not analysed.

6.12 VOXEL BASED MORPHOLOGY

Voxel based morphology (VBM) was performed to examine for any significant structural differences between the groups that may have developed as a result of training.

Initially the 4 defined ROIs were examined using repeated measures ANOVA. As can be seen in Table 6-22, there were no significant main effects of group or time. However there were significant main effects of hemisphere and ROI and a significant hemisphere x ROI interaction.

There were no significant interactions between time x group or time, group, hemisphere and ROI, suggesting that training did not result in any significant structural changes in the 4 ROIs. (Figure 6-57, Figure 6-58, Figure 6-59 and Figure 6-60).

MAIN EFFECTS	F	Sig.
TIME	1.303	0.267
HEMISPHERE	38.616	<0.001
ROI	6.670	0.017
GROUP	1.339	0.260
INTERACTIONS		
TIME x GROUP	0.073	0.790
TIME x HEMISPHERE x GROUP	0.061	0.807
TIME x ROI x GROUP	0.278	0.604
HEMISPHERE x ROI	88.424	<0.001
TIME x HEMISPHERE x ROI	4.751	0.041
TIME x HEMISPHERE x ROI x GROUP	0.217	0.646

Table 6-22: ANOVA results of VBM.

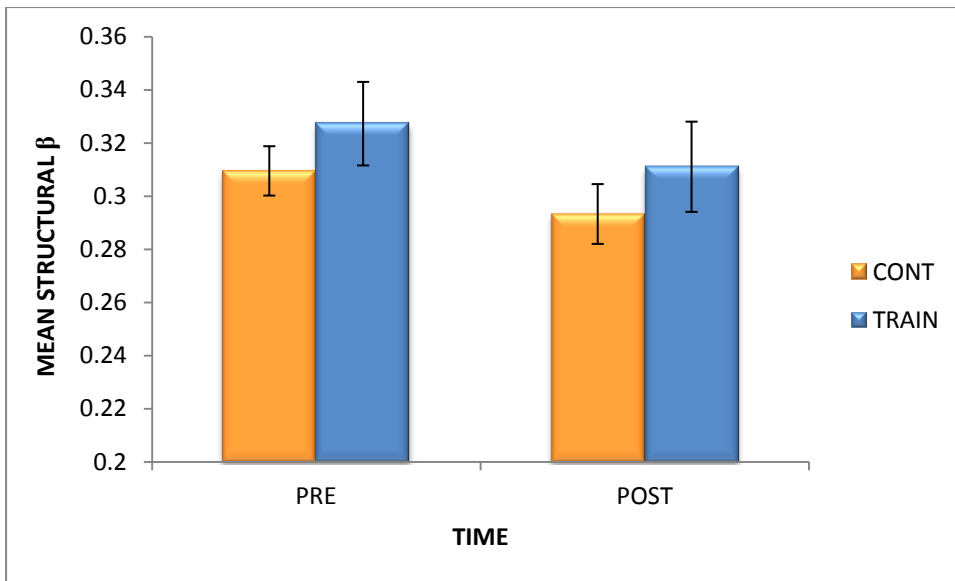


Figure 6-57: RDLPFC- no sig change in structure between groups
Near significant main effect of time ($p=0.053$). Error bars are SEM.

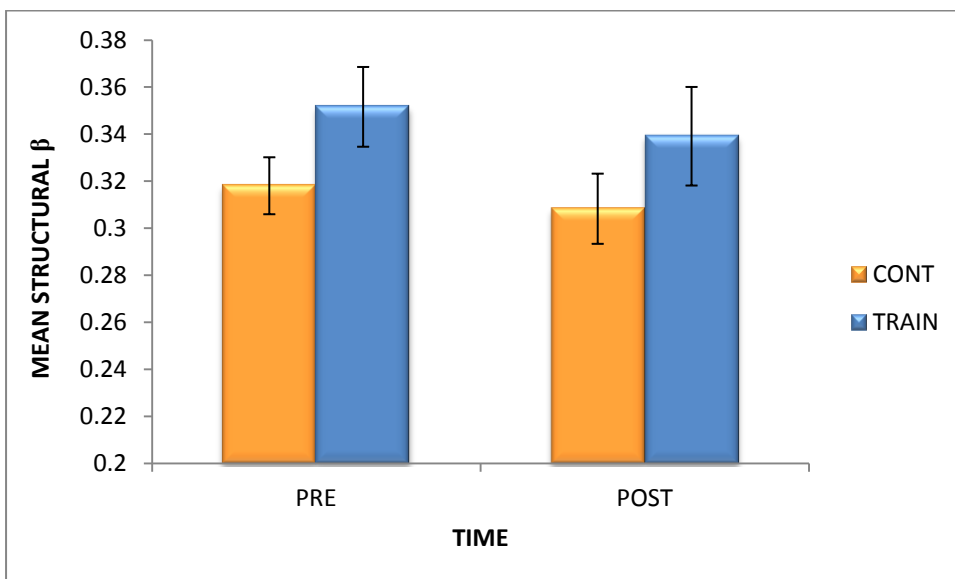


Figure 6-58: Mean β value in the LDLPFC. Error bars are SEM.

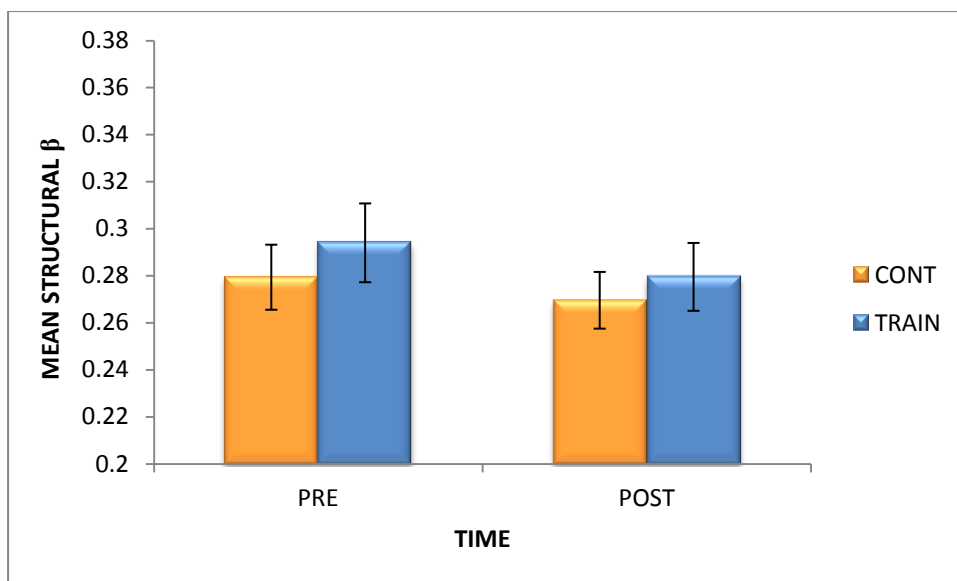


Figure 6-59: Mean β value in the LPC. Error bars are SEM.

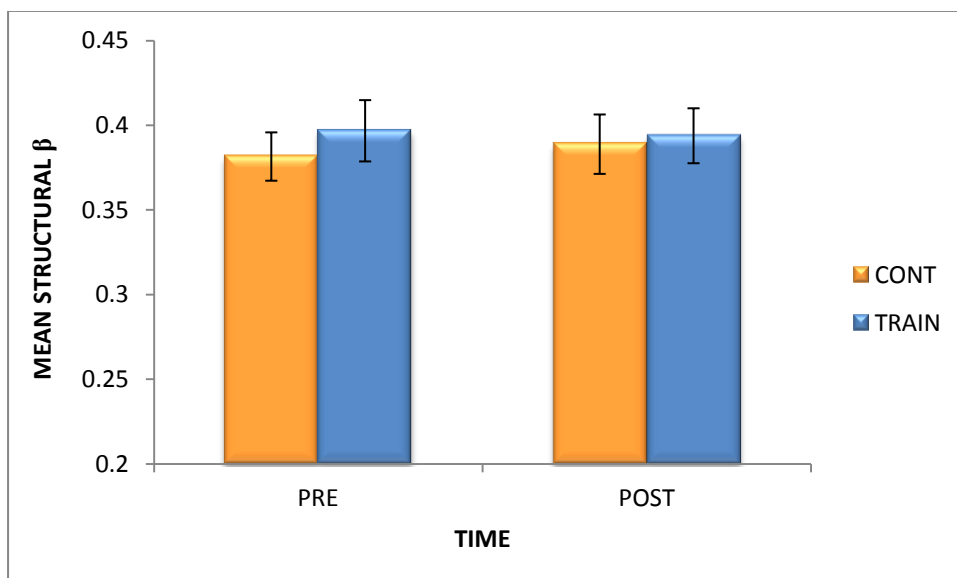
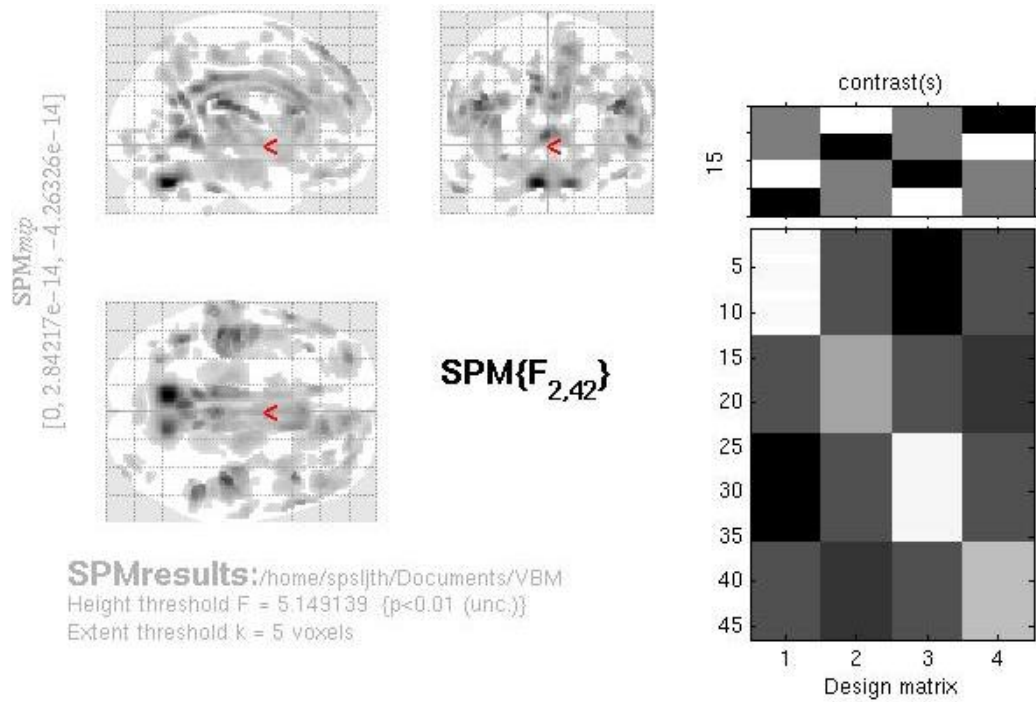


Figure 6-60: Mean β value in the RPC. Error bars are SEM.

6.12.1 WHOLE BRAIN ANALYSIS

Whole brain analysis was examined with F and T contrasts for the main effect of time, and time x group interactions. There was a significant main effect of time ($p_{FWE} < 0.05$) in multiple areas, however no significant time x group interactions. (Figure 6-61, Figure 6-62, Figure 6-63, Figure 6-64, Figure 6-65). Therefore it can be concluded that there was a significant overall effect of time in multiple brain regions, as would be expected in an AD population, however no significant effect of training on underlying brain structure.



Statistics: *p*-values adjusted for search volume

set-level	cluster-level				peak-level					mm mm mm		
	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	F	(Z_{Ξ})	p_{uncorr}			
76	6194				0.000	0.000	43.44	6.44	0.000	-8	-63	-26
					0.000	0.001	29.61	5.62	0.000	12	-64	-26
					0.032	0.036	14.82	4.20	0.000	3	-21	1
	449				0.000	0.001	30.40	5.68	0.000	43	-27	24
					0.015	0.011	18.67	4.66	0.000	37	-19	21
					0.806	0.214	9.40	3.34	0.000	49	-12	19
	416				0.000	0.001	30.15	5.66	0.000	-45	-30	24
					0.000	0.002	27.63	5.47	0.000	-45	-18	21
					0.015	0.011	18.79	4.67	0.000	-48	-9	16
	771				0.000	0.002	28.29	5.52	0.000	-3	-54	4
					0.015	0.011	18.72	4.67	0.000	4	-51	4
					0.991	0.427	7.50	2.94	0.002	3	-67	-6
	106				0.001	0.002	25.71	5.32	0.000	-42	-54	27
	2017				0.001	0.002	25.56	5.31	0.000	-9	-45	33
					0.001	0.002	25.44	5.30	0.000	2	-31	28
					0.001	0.003	24.53	5.22	0.000	-9	-33	39
	77				0.001	0.003	24.32	5.21	0.000	42	17	19
	429				0.002	0.004	23.30	5.12	0.000	51	-46	3
					0.398	0.096	11.58	3.72	0.000	45	-48	16
					0.420	0.100	11.45	3.70	0.000	50	-34	-8
	212				0.004	0.007	21.97	4.99	0.000	49	-40	19
					0.995	0.470	7.26	2.88	0.002	48	-48	30
	102				0.008	0.009	20.20	4.82	0.000	-42	-55	12
	44				0.008	0.009	20.07	4.81	0.000	-14	-60	25

Figure 6-61: SPM of main effect of time F contrast for VBM, demonstrating multiple significant voxels at $p_{FWE} < 0.05$.

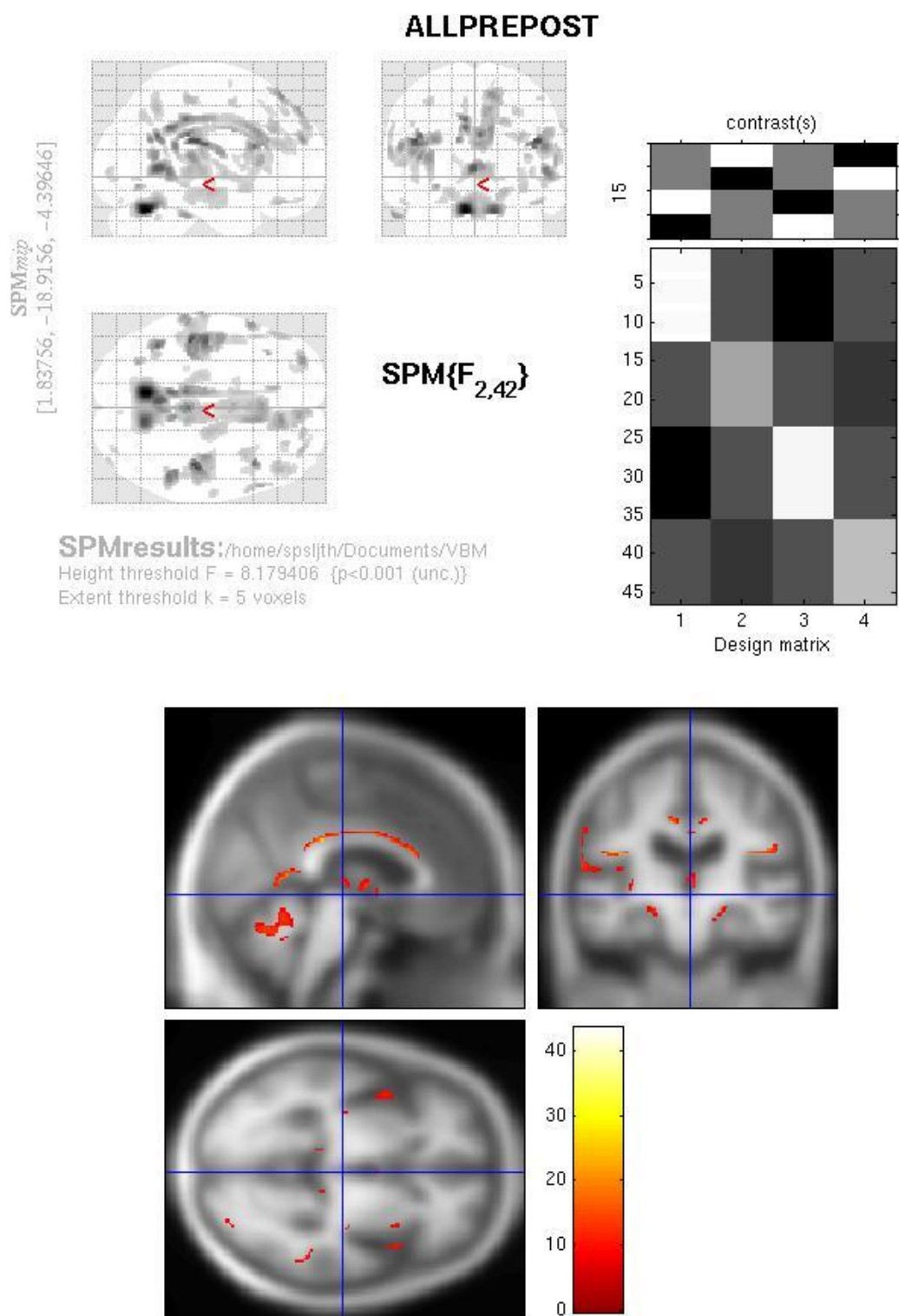
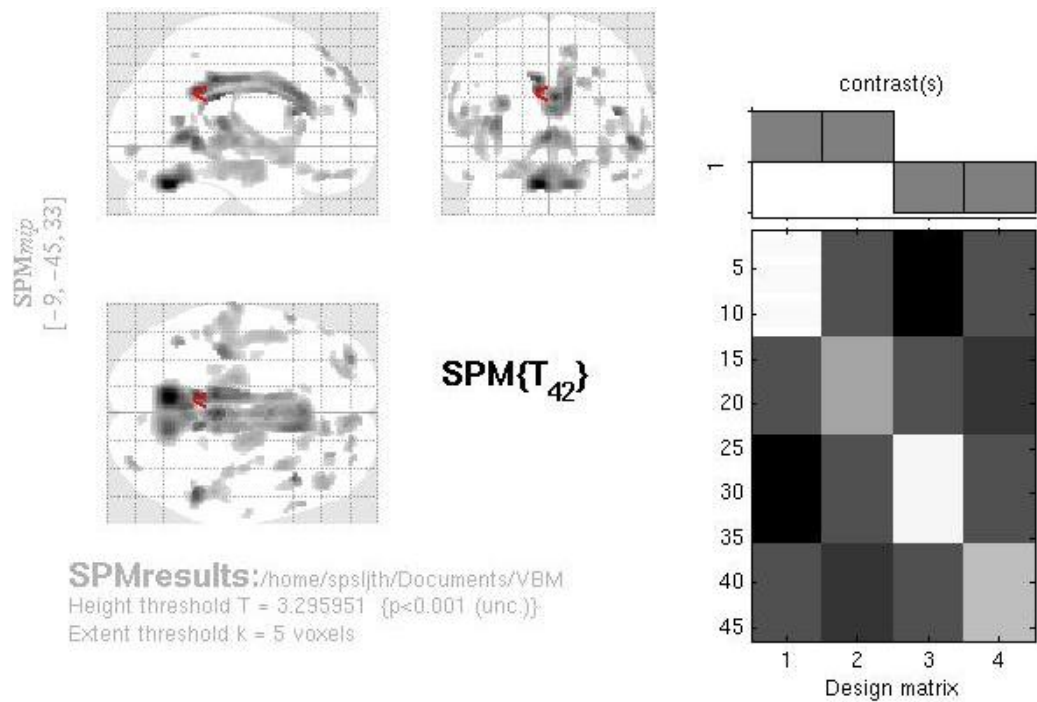


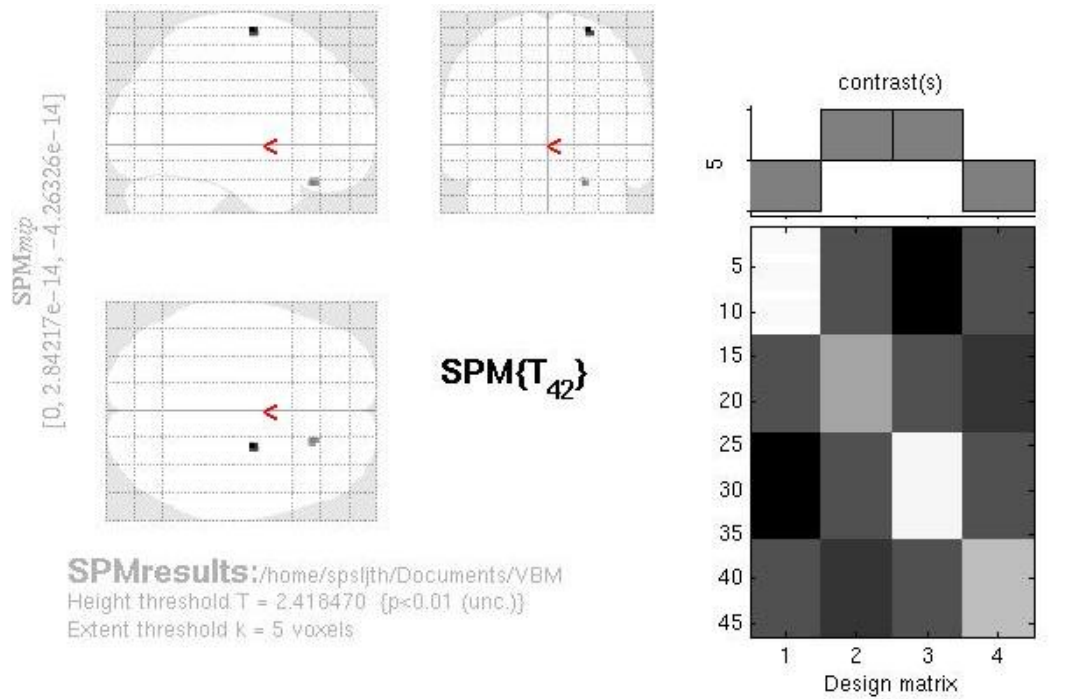
Figure 6-62: SPM of main effect of time F contrast for VBM overlaid on group specific mean structural template.



Statistics: p -values adjusted for search volume

set-level		cluster-level				peak-level					mm mm mm		
p	C	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	(Z_{Ξ})	p_{uncorr}			
0.000	39	0.015	0.330	2065	0.006	0.000	0.001	7.66	6.03	0.000	-8	-63	-26
						0.003	0.035	5.88	5.00	0.000	10	-64	-26
						0.001	0.021	6.37	5.30	0.000	2	-31	28
		0.024	0.330	1779	0.010	0.001	0.021	6.31	5.26	0.000	-9	-45	33
						0.001	0.021	6.27	5.24	0.000	-9	-33	39
						0.003	0.035	5.91	5.01	0.000	51	-46	3
		0.553	0.969	203	0.341	0.267	0.275	4.17	3.79	0.000	50	-34	-8
						0.003	0.035	5.84	4.97	0.000	-2	-54	4
						0.004	0.035	5.78	4.93	0.000	42	17	19
		0.795	0.969	46	0.670	0.011	0.050	5.41	4.69	0.000	-36	-28	12
						0.101	0.157	4.59	4.11	0.000	-34	-24	4
						0.156	0.199	4.41	3.97	0.000	-64	-21	16
		0.082	0.775	1098	0.036	0.023	0.076	5.15	4.51	0.000	-32	54	24

Figure 6-63: SPM of pre > post T contrast at a significance threshold of $p < 0.001$ uncorrected.



Statistics: *p*-values adjusted for search volume

set-level		cluster-level				peak-level					mm mm mm		
<i>p</i>	<i>c</i>	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>k</i> _E	<i>p</i> _{uncorr}	<i>p</i> _{FWE-corr}	<i>q</i> _{FDR-corr}	<i>T</i>	(<i>Z</i> _≡)	<i>p</i> _{uncorr}			
1.000	2	1.000	0.918	16	0.902	1.000	0.849	2.68	2.56	0.005	24	-9	69
		1.000	0.918	12	0.918	1.000	0.849	2.53	2.42	0.008	21	30	-26

Figure 6-64: SPM of time x group t contrast for VBM, demonstrating no significant voxels.

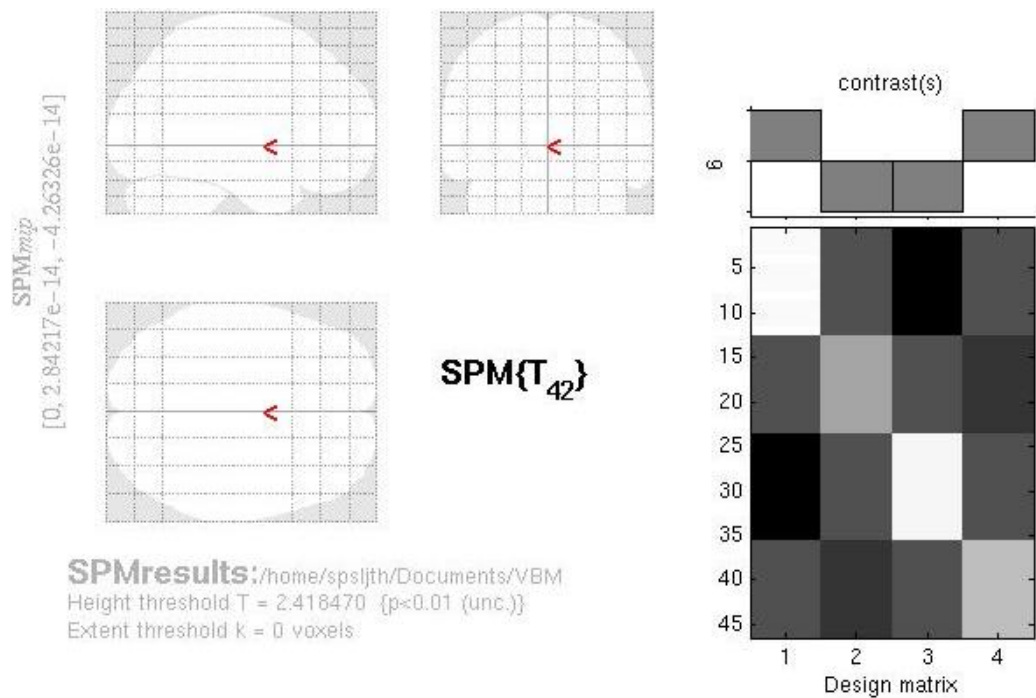


Figure 6-65: SPM of reverse group x time t contrast for VBM, demonstrating no significant voxels.

6.13 PSYCHOPHYSIOLOGICAL INTERACTIONS - CONNECTIVITY ANALYSIS

For the PPI analysis, the seed region was defined as the RDLPFC, with the other defined ROI as the regions of interest (ROI 1 = LDLPFC, ROI 2 = LPC, ROI 3 = RPC).

The estimated PPI values were entered into a repeated measures ANOVA, examining connectivity between the seed region and each of the other ROI separately:

6.13.1 RDLPFC- LDLPFC

MAIN EFFECT	F value	Sig. (p)
TIME	1.273	0.269
TRIAL TYPE	2.383	0.134
GROUP	0.159	0.694
INTERACTIONS		
TIME x GROUP	0.101	0.753
TRIAL TYPE x GROUP	3.915	0.058
TIME x TRIAL	1.625	0.213
TIME x TRIAL x GROUP	0.291	0.594

Table 6-23: PPI results for RDLPFC- LDLPFC

6.13.2 RDLPFC-LPC

MAIN EFFECT	F value	Sig.(p)
TIME	0.067	0.798
TRIAL TYPE	1.538	0.226
GROUP	0.029	0.865
INTERACTIONS		
TIME x GROUP	0.108	0.745
TRIAL TYPE x GROUP	0.221	0.642
TIME x TRIAL	1.155	0.292
TIME x TRIAL x GROUP	4.087	0.053

Table 6-24: PPI results for RDLPFC-LPC

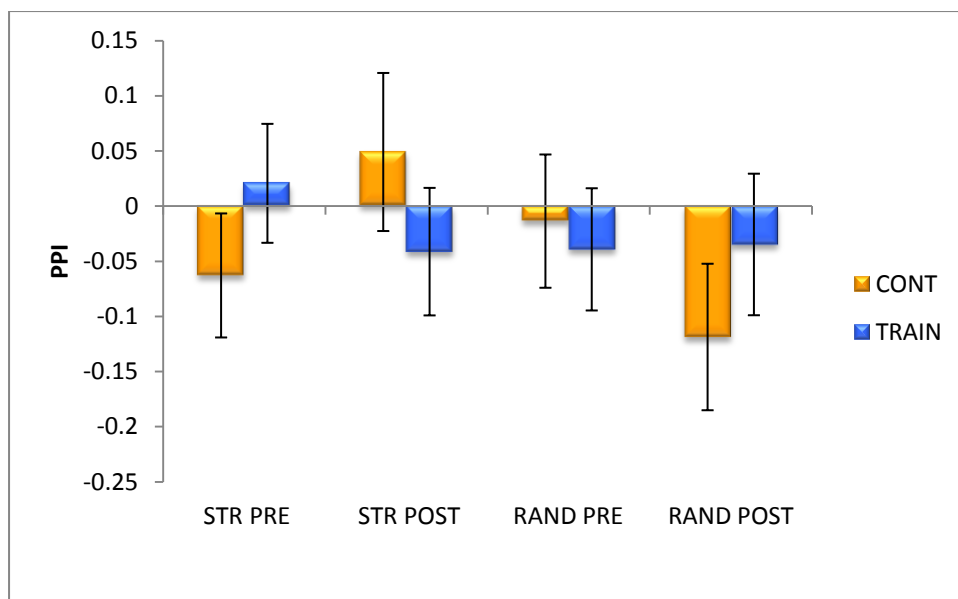


Figure 6-66: PPI results for RDLPFC- LPC by trial type, time and group.

Therefore the PPI between the RDLPFC and LPC shows a near significant group x trial type x time interaction $p = 0.053$.

6.13.3 RDLPFC- RPC

MAIN EFFECT	F value	Sig.(p)
TIME	0.274	0.605
TRIAL TYPE	0.888	0.354
GROUP	0.250	0.621
INTERACTIONS		
TIME x GROUP	0.143	0.709
TRIAL TYPE x GROUP	1.913	0.178
TIME x TRIAL	0.423	0.521
TIME x TRIAL x GROUP	1.135	0.296

Table 6-25: PPI results for RDLPFC-RPC

Chapter 7 DISCUSSION

7.1 CHUNKING IN WORKING MEMORY

As described in Chapter 1, the Baddeley and Hitch model of working memory (WM) describes two limited capacity subsidiary systems, the phonological loop and visuo-spatial sketchpad. Above these subsidiary systems are the central executive and episodic buffer. These higher-level components provide attentional and executive control and resources to the more passive lower-level systems^{16 19}. As WM capacity appears to be limited to only a few items of information²³, humans use executive strategies to enable these items held in WM to be complex mental representations. Chunking, despite its conceptual simplicity, is a major strategy behind our ability to form such complex mental representations. By recognising or enforcing patterns on information, and compressing it into a more efficient state, chunking enables us to create, assess and manipulate these complex chunks within the limited workspace of WM.

Seen in this light, our use of chunking is almost limitless. Language is an example of the chunking of individual letters to form words. A more complex example is the chunking and binding of sensory inputs with semantic and episodic memories that forms many of our subjective conscious experiences, such as recognising a friend..

Chunking therefore has a profoundly powerful and ubiquitous role in how we experience and interact with the world. In the words of Bor ‘*Chunking can vastly increase the practical limits of WM; it is the secret master of this online store, and the main purpose of consciousness*¹⁷⁸. To Bor, and other theorists like Bernard Baars, WM and consciousness are largely synonymous, as ‘*consciousness boils down to the information sitting right now in our WM*^{178 179}’.

In the current study, participants were trained in chunking using a very simple task: structured digit spans. Although an extremely simple training paradigm was used, the concept behind its hypothesised and observed efficacy lies not in teaching a new compensatory technique, but in harnessing and directing this pre-existing and powerful strategy to increase the practical limits of WM. The evidence from the cognitive training literature in healthy adults, and from the meta-analysis of AD trials in Chapter 2, suggests that training effects appear limited to trained tasks. ‘Far transfer’, i.e. the

transfer of training-related benefit to unrelated non-trained tasks, is the exception rather than the norm^{50 180}. Even some of the apparent exceptions may actually be due to underlying similarities between outcomes, particularly in WM training¹⁸⁰. This is because WM clearly overlaps and enhances many other cognitive processes. For example, information to be encoded in episodic memory will first be held in WM, and recalled episodic memories will also be subjectively experienced and manipulated using WM resources. There is also overlap at a neural network level, as the brain regions most consistently associated with WM, namely the pre-frontal cortex (PFC) and posterior parietal cortex (PPC) network, are also associated with a range of 'higher level' executive processes^{45 176} and have been implicated as neural correlates of consciousness¹⁸¹.

In this study, improvements in a range of tasks were hypothesised, as chunking is an executive strategy that can be applied to different types of information.. The study found an improvement in the training task, where stimuli were designed to be easy to chunk. However, the study also demonstrated that other verbal material, such as word recall lists in the ADAS-Cog or short story segments in the verbal episodic memory tests were also improved by training in chunking.

There were no improvements in the performance of tasks assessing executive function, suggesting that rather than leading to overall executive improvements *per se*, training led to a specific enhancement of the executive strategy of chunking itself. Furthermore, the specificity of the verbal effects, compared to the lack of training effects on spatial WM and spatial episodic memory tasks suggests that the chunking training effect was limited to the verbal modality. In other words, although this study demonstrated that specific cognitive training can 'work' in early AD, and that training generalised to untrained tasks, the observed benefits were most likely due to an increase in efficiency of the inherent ability to chunk verbal information, rather than any increase in non-verbally measured cognitive ability or intelligence.

At a neurobiological level, the PFC- PPC network is associated with the use of chunking strategies, with evidence for increased activation during the explicit search and formation of new chunks or patterns^{24 27}. There is also evidence that activity in this network decreases when such chunks have formed, patterns or rules have been established, and behaviour becomes more implicit¹⁸². The fMRI data from the current study demonstrated that training in chunking is associated with changes in BOLD activity, suggesting training-related functional plasticity in early AD. As is discussed in more detail below, the observed post- training decrease in activation is consistent with a cognitive shift from

explicit to implicit processing and an improvement in efficiency at a neurobiological level. Importantly, this study demonstrated these effects in the context of behavioural change in participants with AD.

7.2 SPECIFIC AIMS OF THE STUDY

The specific aims of the study and the interpretation and implications of the results are now discussed in more detail. The *a priori* hypotheses of the study were that:

- 1) Training individuals with early AD in the use of chunking strategies would improve their WM capacity.
- 2) Following training in chunking, improvement in WM capacity would generalise across different modalities of WM tasks and measures of general cognitive functioning.
- 3) Improvement in WM capacity following cognitive training would be associated with re-organisation of functional activity in the prefrontal cortex and posterior parietal cortex.

7.3 DID CHUNKING TRAINING IMPROVE WM CAPACITY IN INDIVIDUALS WITH EARLY AD?

The first hypothesis was based on pilot results suggesting that participants with early AD could use chunking to improve their WM⁶⁸. Therefore, before examining the results of training it is important to establish whether there was evidence of a chunking effect at baseline.

At baseline, participants performed significantly better on structured compared to random trials on both verbal and spatial span tasks. Therefore, performance at baseline is consistent with previous results in healthy young and older people, and participants with early AD^{24 26 68}. This suggests that participants did use chunking strategies, and that the tasks were sufficiently sensitive to detect differences between the structured and random trial types.

It is an assumption that the performance benefits seen with structured trials were due to participants using the intrinsic numerical 'chunks' or spatial shapes inherent in the structured sequences. This assumption is based on previous work in young adults, where it was verified that structured sequences encourage chunking^{24 26 27}. It is entirely possible, however, that the strategy used by

participants in the current study was chunking based not on the inherent structures provided, but on chunking the information differently (e.g. chunking the first pair of numbers and second trio of numbers irrespective of any structure) or using an alternative chunking strategy such as associating numbers with personal memories or facts¹⁸³. Prior to baseline testing, there was no discussion with the participant about trial type or strategy; therefore they were not led in any way to use a specific strategy. Previous studies have examined potential strategies used during structured and random digit span performance and have shown that a range of chunking strategies can lead to improved digit span performance²⁷. It is therefore reasonable to hypothesise that chunking was the main effective strategy used with structured trials in the current study.

7.3.1 IMPROVEMENT IN VERBAL WM PERFORMANCE

WM training led to a significantly greater increase in digit span score compared with the control intervention, both when averaged across all trial types ($p = 0.040$ (1 tailed)) and in structured trials only ($p = 0.017$). Structured trials improved significantly more in the training group than the control group. Random trials also improved more in the training than the control group, but not significantly. Therefore the primary hypothesis was confirmed: training led to a significant improvement in WM score. This effect was more significant with the structured trials, which encouraged chunking and were the focus of the training intervention, than in random trials.

As discussed above, a cognitive interpretation of this increase in score is that by using chunking, participants were able to increase their verbal working memory capacity. In terms of the Baddeley model of WM^{15 16 19}, this may be explained by the more implicit systems of the visuospatial sketchpad or phonological loop increasing their intrinsic storage capacity. However a more likely explanation is that chunking allowed more items of relevant information to be held in WM, without an underlying increase in capacity *per se*. To facilitate this, attentional and executive resources of the central executive system and episodic buffer were recruited to bind the relevant bits of information into 'chunks', by recognising intrinsic patterns in the digit sequences or interfacing with episodic and semantic memory processes that access additional relevant information¹⁹. For example an important date that can be linked with the digit sequence presented, or a rhyme like '2-4-6-8 who do we appreciate'^{19 184}. This may initially involve an explicit process, requiring the participant to be consciously aware of these links.

As the more executive components of the working memory model (e.g. central executive and episodic buffer) appear to be impaired earlier in AD than the passive systems (e.g. visuospatial sketchpad and phonological loop)^{17 21}, it is noteworthy that the AD participants in this study were able to benefit from WM training that focused on the use of an executive strategy. This suggests that the use and training of executive strategies can still be effective in early AD.

7.4 DID CHUNKING TRAINING LEAD TO IMPROVEMENTS IN NON-TRAINED WM TASKS AND GENERAL COGNITIVE FUNCTIONING?

There was no significant effect of training on performance of the spatial span tasks, either on overall score or ability to chunk. Both groups increased their span scores but there were no significant differences between the groups or trial types.

This suggests that the WM improvement was limited to the verbal domain. This may be interpreted as evidence for a selective training effect on the phonological system within working memory, rather than on a more general central executive component. There is evidence for neuroanatomical dissociation of verbal and visuospatial processing within WM^{37 185 186} and it may be that the underlying functional neural networks that were strengthened by training were specific to verbal processing. However the evidence that there were also generalised improvements in non-trained tasks, suggest that the effects are not specific to verbal WM alone.

7.4.1 DID TRAINING EFFECTS GENERALISE TO GENERAL COGNITIVE MEASURES?

Importantly, both the MMSE and ADAS-Cog showed a significant improvement following training, compared to controls. Therefore there was evidence of generalised improvement in cognitive function following training.

This is an important finding due to the limited evidence that cognitive training produces generalised improvements on non-trained tasks¹⁸⁷. It also suggests that the underlying cognitive processes learnt during training (chunking) and/or the functional plasticity resulting from training, supported

performance of cognitive tasks apparently unrelated to the training regime. Within the ADAS-Cog, there is the potential to explicitly use chunking strategies to improve performance, particularly on the word recall section of the test, where participants have to encode and then recall a list of 10 words⁷². Although the words are superficially unrelated, it may be possible to use chunking to link the words and improve recall. Examination of the ADAS-Cog data in the training group revealed that participants improved in their word recall sub-score, which may be evidence for this explanation.

7.4.2 DID TRAINING EFFECTS GENERALISE TO IMPROVEMENTS IN EPISODIC MEMORY?

There was a significant improvement in verbal episodic memory in training participants compared to controls, but no significant changes were seen in visuospatial episodic memory following training. This mirrored the WM results, where verbal but not spatial WM significantly improved with training. Chunking may have been used to improve episodic memory, by chunking aspects of the story to be remembered in the logical memory tasks. It would be more difficult to apply chunking strategies to the Paired Associates Learning task, which may be why there was no improvement seen on this task. There is some evidence of the overlap between WM and episodic memory processes both cognitively and neuro-anatomically^{188 189} and therefore it may be that the improvement in WM encoding with chunking training facilitated improved episodic memory encoding and recall, resulting in the observed training-related verbal episodic memory benefits.

7.4.3 DID TRAINING EFFECTS GENERALISE TO IMPROVEMENT IN EXECUTIVE FUNCTION?

There were no significant effects of training on performance of any of the executive function tasks, which encompassed a range of planning, reasoning, response inhibition and set shifting functions. Although the MD network and a PFC-PPC network have been implicated in executive function, and also in tasks putatively assessing fluid intelligence^{190 191}, it is notable that despite evidence of training-related plasticity in this network in the current study, there were no behavioural improvements on executive function tasks. A number of factors underpin fluid intelligence¹⁹², and there is considerable overlap between the cognitive processes and the functional neuro-anatomy involved in a variety of attentional, working memory and executive functions⁴⁵. Therefore, the lack of generalised executive

function improvement suggests that chunking training did not improve 'executive function', but rather affected more limited and specific WM processes. Alternatively it may be that any executive improvement was either too small or too specific to be picked up by the range of executive tasks used in this study. The most likely explanation, however, is that training resulted in an improved ability to specifically use chunking strategies, and it may have been more difficult to apply these strategies to tasks of executive function, with the exception of the verbal fluency task.

There were also no significant training effects on sustained attention. This suggests that the improvements seen in verbal WM, episodic memory and general cognitive function were not simply due to an underlying improvement in sustained attention. However this result differs from other studies which have demonstrated that WM training can lead to improvements in sustained attention¹⁹³.

7.4.4 DID TRAINING HAVE ANY IMPACT ON ACTIVITIES OF DAILY LIVING OR QUALITY OF LIFE?

There were no significant effects of training on performance of Instrumental Activities of Daily Living (IADLs) or on the Dementia Quality of Life scale (DEMQOL). Although not reaching significance levels, both groups did demonstrate an increase in score on the DEMQOL. This supports the finding in the literature that cognitive training is acceptable and improves quality of life rather than causing frustration or anxiety^{110 194}.

The IADL may have been too insensitive a measure of functional ability to capture any improvements following training. Functional decline at the very early stages of AD may be subtle^{195 196}, and combined with the fact that the IADL measure in this study was used to reflect perceived rather than clear objective functional ability, it is unsurprising that no functional change was detected over 8-12 weeks. However there was a non-significant increase amongst the training group on the IADL score. Therefore it may be that participants did experience improvements in everyday functioning that were not picked up by the measure (anecdotally one training participant reported significant improvement in his golf performance that he attributed to training!)

7.5 INTERPRETATION OF BEHAVIOURAL RESULTS

At the behavioural level, an important basic issue is identifying whether improved performance on a cognitive task actually reflects genuine improvement in the underlying cognitive function. Even though the current study used an active control group to mitigate against non-specific practice effects, a further confounding issue is discerning what is actually being tested during an individual task. For example, even the simplest digit span task requires resources of sustained attention, understanding of the instructions given, planning of responses, inhibition of irrelevant distractions and monitoring of behaviour. A highly complex executive task will similarly require lower level resources of sensory processing, sustained attention, and potentially verbal or motor responses. The cognitive tests used in the current study are well established and have been validated to assess specific cognitive domains, however there are no 'pure' cognitive tests. As stated above, even tasks that are superficially dissimilar and indicate 'far transfer' may not be demonstrating this at all, rather a non-specific improvement in a participant's willingness to cooperate or ability to sustain attention for long enough to complete the tasks¹⁸⁰. This may be especially true in an AD population, whose performance on neuropsychological tasks may fluctuate and be more susceptible to non-specific effects of fatigue or anxiety than healthy young participants. However the consistent pattern of results found within tasks attributed to the same domains, and use of repeated measures analysis provides evidence for the validity of the behavioural findings in this study.

7.6 WAS CHUNKING TRAINING ASSOCIATED WITH CHANGES IN FUNCTIONAL ACTIVITY IN THE PFC AND PPC?

Overall there was a significant effect of training on functional activity in bilateral prefrontal and parietal regions. The control group increased in activation, whilst the training group reduced in activation. This overall training effect was more significant for structured trials ($p = 0.028$) than when averaged across both trial types ($p = 0.059$).

When examined by region of interest, there was a significant effect of training in the right dorsolateral prefrontal cortex (RDLPFC) when structured trials were examined ($p = 0.045$) and near-significant effects across both trial types ($p = 0.06$). The left parietal cortex (LPC) demonstrated significant training-related changes, and the right parietal cortex (RPC) near significant training-related changes with structured trials ($p = 0.04$ in LPC and $p = 0.054$ in RPC).

There was therefore a consistent pattern of training-related deactivation in all four regions of interest, contrasting with increased activation in all four regions in the control group.

Sensitivity analysis examining all trials (basic model) and multiple demand (MD) regions¹⁹⁷

demonstrated further evidence of a consistent training-related pattern of functional plasticity - with training resulting in a decrease in activation with time, compared to an increase in activation in the control group. The significant training effects in the RDLPFC were also replicated in the analysis of all trials, and with structured trials in the right anterior inferior frontal area of the MD network.

Whole-brain analysis of the effects of training showed several predominantly frontal regions reaching an uncorrected significance level ($p < 0.01$), with a reduction in activation as a result of training. An exploratory sub-cortical ROI analysis demonstrated an increase in activation for both trial types in the control group, but in the training group activation was increased for random trials and decreased for structured trials.

There were no significant effects of training on functional activity during the delay phase of the task; however the pattern of activation change from the encoding phase persisted - with training leading to a reduction in activation compared to an increase in activation in the control group. Examining effects across the whole brain, one occipital cluster reached significance ($p_{FWE} < 0.05$), again demonstrating reduced activation following training.

Therefore the consistent pattern of training-related plasticity was of a decrease in functional activity in all cortical areas and a trial-dependent training effect in subcortical regions with structured trials demonstrating a decrease and random trials an increase in activation.

This was in contrast to increased activation in all examined cortical and subcortical areas in control participants between the baseline and follow up scans.

This pattern of results is consistent with the growing literature reporting that cognitive training leads to a decrease in cortical functional activity⁶³. A useful analogy for this has been provided by Petersen *et al* (1998)¹⁹⁸. They suggest that there is a scaffolding-storage framework that is built up during cognitive training. Initially a task requires large attentional and executive resources in order to be successfully performed, and is a predominantly explicit process. This executive resource is underpinned by a 'scaffold' of cortical regions, including the prefrontal cortex (PFC), anterior cingulate cortex (ACC) and posterior parietal cortex (PPC)^{63 198}. As described in a review by Kelly and Garavan, at the initial stages of training these cortical areas 'perform the scaffolding role'⁶³. The role of the PFC in performing this executive and attentional 'scaffolding' is consistent with theories of PFC function¹⁹⁹ and also animal models, demonstrating decreased activity in the neurons of the PFC with learning^{63 200}.

As training continues, the requirement for attentional and executive resources diminishes, and therefore activation in this network correspondingly decreases as the 'scaffolding falls away'^{63 198}. This may coincide with a coordinated increase in activity within areas underlying task-specific processes. This has been demonstrated in motor learning paradigms, where initial PFC, AC, PPC and premotor activation decreased with training and an increase in motor cortex and cerebellar activation emerged, as the tasks under examination became more practised and automatic²⁰¹⁻²⁰³.

An interpretation of these patterns of training-related cortical deactivation has been of 'neuro-physiological pruning from attention-demanding explicit processes to more automatic procedural processes'^{63 198 204}

A number of potential neurobiological mechanisms have been suggested to facilitate this plasticity. At a synaptic level the formation of new synapses or strengthening of existing synapses may occur^{205 206}. Changes in the intrinsic excitability of neurons²⁰⁷, or in activation patterns at the level of neural networks²⁰⁸ may also contribute to plasticity. Poldrack (2000) has speculated that such effects may lead to increased efficiency by resulting in a *'sharpening of the responses in a particular neural network with experience...(so that)... a minority of neurons would fire strongly to a particular stimulus or task'*²⁰⁴

A summary of previously reported effects of training on cortical and subcortical areas is shown in Table 7-1. Many of the studies examining the effects of practice have described a decrease in cortical

activation within the course of a single session^{62 209-211}. This suggests that functional redistribution can occur over short timescales of around an hour. However other studies have also demonstrated similar redistribution dynamics that developed over longer training periods of several weeks^{177 212 213}. This was the case in the current study, where the observed changes in cortical activation were observed following an average period of 82 days. As the current study was not longitudinal it cannot answer the question of whether such redistribution over longer periods may be longer lasting, or be the consequence of more permanent underlying neuronal processes. However, longitudinal cognitive training studies in healthy older adults have found long lasting training effects, with limited booster training, which suggests this may be a possibility^{57 214}.

The initial increase in activation in the PFC-PPC network predicted by the scaffolding/efficiency theory may also explain the results observed in control participants. Although these participants were exposed to an active control intervention, this was a low level demand task of only three digits. Therefore the five digit span task performed in the scanner would represent a considerable increase in task difficulty from the control intervention. In keeping with this theory, control participants would require increased executive resources to perform the five digit task, which would be reflected in increased PFC-PPC activity, in contrast to the training participants, who had been adaptively trained. However, while this may explain an increase in activity in the PFC-PPC in untrained participants performing the WM task, the observation that the activation in control participants increased from baseline to follow up, rather than remaining at a constant level, needs to be explained. It has been observed that, in line with the efficiency theory, activation in PFC and PPC areas may follow an inverted U-shaped quadratic function, with activity increasing early in training, prior to decreasing²¹². It is probable that control participants, due to the low level training they received, were still at a point near the top of the inverted U shaped curve, and that adaptive training led to participants in the training group being much further along the curve with decreasing activation being observed²¹². It may also be that the increase in activity reflects the improved span performance seen in controls, as they may have been more engaged and trying harder at the task at follow up compared to baseline. As has been suggested, according to the efficiency theory, training leads to decrease in cortical activation as the procedure becomes increasingly implicit. Reflecting this, there may be an increase in activation elsewhere in the distributed network underlying task performance.

As shown in Table 7-1, some studies of cognitive training involving WM or other higher-level cognitive training have demonstrated a decrease in cortical activation but an increase in subcortical activation with training¹⁷⁷. Subcortical areas are implicated in more implicit processes²¹⁵, which would be in keeping with the overall theory that practice results in a transfer from initial attention heavy explicit to less executive and more implicit processes.

It has been suggested that changes in connectivity both within and between brain areas are important in functional redistribution observed within training²¹¹. The decrease in cortical activity may be associated with a decrease in connectivity between separate cortical regions as they become more efficient, and an increase in functional connectivity between cortical and subcortical regions^{64 211}.

This fits with the results of the current study - where training resulted in decreased cortical activation, and decreased connectivity between PFC and PPC regions, as chunking became more learned and implicit. Although there were no significant training-related changes in functional connectivity (as measured by PPI values) between the RDLPFC and the LDLPFC or RPC, there was a near-significant time x trial x group interaction between the RDLPFC and LPC ($p=0.052$). In the training group the PPI value reduced for structured trials, however increased non-significantly for random trials. This may reflect a reduction in connectivity that corresponds to the reduced executive load required to perform structured trials following training.

Evidence in support of this is found in a study by Fletcher *et al.*, whereby a decrease in right fronto-parietal connectivity was demonstrated with rule learning during an artificial grammar task; however these authors also found an increase in connectivity between left and right PFC²¹⁶.

The exploratory subcortical results in the current study do not clearly reflect an increase in activation as learning is established, and therefore do not convincingly fit into the pattern reported by Dahlin *et al.*¹⁷⁷. This may simply reflect a lack of power to identify such effects in the current study, or may reflect a difference in training-related plasticity in older adults or in AD.

Critically however, the current study provides evidence of the potential for functional plasticity following training in an Alzheimer's population. Functional plasticity is increasingly reported in older adults and in MCI^{61 217}; however the extent to which training-related plasticity is possible in AD remains unclear. These findings provide important support for continued plasticity in the early stages of dementia.

STUDY	TASK	TRAINING	TRANSFER	FRONTO-PARIETAL	SUBCORTICAL
CHUNKING (not training studies)					
BOR et al 2004 ²⁶	Digit Span Str vs. Rand trials	n/a	n/a	Increased during encoding	Caudate nucleus increased in encoding
BOR et al 2003 ²⁴	Spatial chunking Str vs. Rand trials	n/a	n/a	Increased	n/a
WM TRAINING					
DAHLIN et al 2008 ¹⁷⁷	WM 'updating'	15 sess (5 wks) T=16, C=7 (young healthy)	To non-trained updating tasks	decreased	Increased
WESTERBERG et al 2007 ²¹³	WM- visual WM, Backward DS and letter span	25 days (5 wks) T=3, C=11 (young healthy)	To visuospatial memory and reasoning	Increased	n/a
OLESEN et al 2004 ⁵³	WM- spatial	20 days (5 weeks) T=11, C=11 (healthy elderly)	To stroop test and IQ,(Raven's matrices)	Increased	Increased
ERICKSON et al 2007 ²¹⁸	Dual task	5 sess (2-3 wks) T=16, C=15 (healthy elderly)	no	Decreased	No change
GAAB et al 2006 ²¹⁹	Pitch memory	5 sess (5 days) T=14, C=10 (young healthy)	no	Decreased	Increased
HEMPEL et al 2004 ²¹²	n-back	Daily for 4 wks T=9, C=0 (healthy)	no	Increased at 2 weeks, decreased after 4 weeks	
BREHMER et al 2011 ¹⁹³	Adaptive WM training (visuospatial) Active controls	25 x 25min sess (5 wks) (healthy elderly)	to non-trained WM tasks and sustained attention	decreased	Increased (Activation change correlated with behavioural improvement)
SINGLE SESSION					
PETERSEN et al 1998 ¹⁹⁸ ²¹⁹ ENREF_222	Verbal production task Motor (tracing maze)	1 sess novel task, 10 min practice and novel task after practice	n/a	Shift in activity from frontal, AC and cerebellum to sylvian-insular cortex'	
JANSMA et al 2001 ²⁰⁹	Verbal WM	Single session- 45	n/a	Decreased	

		min of practice, T=15 (healthy)			
GARAVAN et al 2000 ²¹⁰	Visuospatial WM (delayed match to sample)	Single session- scanned during trial runs 1-4, 21- 24 and 41-44 T=12	n/a	Decreased	n/a
BUCHEL et al 1999 ²¹¹	Associative object-location learning	Single session Comparing early and late per session		Decrease but increase in effective connectivity between dorsal and ventral visual pathways	n/a
LANDAU et al 2004 ⁶²	Visual WM (faces)	Single session- early to late in scanning session across low or high memory loads	n/a	Decreased	
IN HEALTHY ELDERLY/ MCI/ AD					
HAMPSTEAD et al 2012 ²²⁰	Mnemonic training	3 sessions 18 MCI 16 healthy elderly		Analyses restricted to hippocampus. MCI- increased activity following training. Control group decreased activity. Healthy elderly: Decreased activity in exp group, no change in control group	
Van PAASSCHEN et al 2013 ²²¹	Cog rehab (face-name pairs)	8 weeks T=7, C=12	No behavioural change	Exp: Increased Cont- decrease	increased

Table 7-1: Summary of fMRI findings in chunking and cognitive training studies

T=training participants, C= control participants, sess= sessions, wks= weeks, MCI= mild cognitive impairment

7.7 WERE BEHAVIOURAL CHUNKING EFFECTS ASSOCIATED WITH ANY CHANGE IN FUNCTIONAL ACTIVITY?

There were no significant differences in functional activation in the regions of interest between structured or random trials at baseline. Therefore although there was a significant difference between behavioural performance on structured and random trials, this was not reflected in any underlying significant differences in activation in the ROIs. There was a significant time x trial type x group interaction in the LPC ($p = 0.04$), and when structured trials were examined independently, there were significant or near significant time x group interactions in the RDLPFC, LPC and RPC. This was in contrast to no significant time x group interactions when random trials were examined independently. These results reflected the trend of greater reduction in activation with structured compared to random trials in the training group.

In the whole brain analysis, there were clusters of increased significance in the parietal cortex (BA40) and occipital regions for the random compared to structured trials

Therefore the results during encoding demonstrated the opposite effect to that seen in chunking studies in healthy young participants^{24 26}, whereby chunking was associated with an increase rather than decrease in DLPFC and PPC activation, however this difference did not reach significance in the current study.

During the delay phase, however, the pattern of activation with chunking was of increased activation across all 4 ROIs for structured compared to random trials. Therefore the delay phase showed a reversal in the pattern of chunking effects, with structured trials showing an increased activation compared with random trials. Interpretation of these data needs to be made with caution, as none of the group and time interactions were significant.

It is possible that the chunking activation pattern differs from that seen in younger patients due to task difficulty effects. It has been found that activation during episodic memory tasks increases with task difficulty^{155 156}, and a number of further studies have demonstrated how increased task difficulty or load is associated with increased BOLD activation^{222 223}. This may explain the relatively greater

activation seen with random compared with structured trials during encoding. Consistent with this, the behavioural evidence both during and outside the fMRI sessions was that participants scored lower on random trials compared with structured trials, which is likely to reflect that they were more difficult. An alternative explanation is that the increased activation seen with chunking in previous studies in healthy young participants reflected a more explicit, conscious awareness of the intrinsic patterns within the structured trials. In contrast AD participants in the current study, although using chunking, may have been doing so more implicitly, resulting in the activation changes reflecting task difficulty rather than explicit use of chunking.

7.8 WERE THERE ANY GROUP OR TRAINING-RELATED STRUCTURAL DIFFERENCES?

Voxel based morphology analysis demonstrated no significant baseline, post intervention or training-related differences between groups, either in ROI or whole brain analysis.

There was a significant overall effect of time on whole brain analysis, with multiple areas demonstrating a reduction in size with time, however there were no significant time by group interactions. The observed significant effect of time would be expected in an AD population²²⁴, however no significant effects of training were found on underlying brain structure.

This means that the reduction in activation in the training group cannot be explained by a differential reduction in the size of the examined ROIs in the training group during the study compared to controls.

7.9 WAS USE OF CHUNKING EXPLICIT OR IMPLICIT?

Explicit awareness of strategy use and performance was assessed in three ways. Firstly by the meta-memory in adulthood (MIA) questionnaire, particularly the strategy sub-score, secondly by examining subjective reporting of strategy use and performance during testing blocks and thirdly by confidence reporting on a trial by trial basis during fMRI scanning.

Firstly, on the MIA questionnaire, training participants significantly improved their score on the strategy sub-score compared with controls, suggesting a perceived increased use of strategy following training. However this assesses a generic sense of increased strategy use and does not necessarily refer to a participant's use of chunking or other strategies during the training or outcome assessments.

Secondly, subjective reporting of strategy use and performance at baseline revealed that the majority of participants did not report using chunking and noticed no difference between trial types, despite performing significantly better on structured compared to random trials. This suggests that the advantage on structured trials was more of an implicit than explicit process.

Thirdly, although participants were generally poor at monitoring their performance during the blocks of trials during testing, they were accurate on a trial by trial level, with an 80.7% correct matching of confidence report to performance for both groups. Of note, both groups were more accurate at predicting performance with structured than random trials.

Following training, the percentage of participants in the training group who reported that structured trials were easier than random increased (from 20% to 40%), however the majority still failed to notice a difference between trial types. Training participants who stated that they used chunking marginally increased; however the majority still reported not using chunking or other strategies. Training participants improved at correctly monitoring performance during testing, however again over half incorrectly matched perceived with actual performance during testing. Correct monitoring of performance on a trial by trial basis improved marginally in both groups, however the training group improved at correctly monitoring structured trials, but not random trials. In contrast, control participants improved in correctly monitoring random, but not structured trials.

The most striking finding in this data, was that despite scoring higher on a strategy score post training, participants did not significantly report using chunking after testing sessions, nor did the majority seem to find structured testing easier than random, despite having trained for 18 sessions and performing better on structured compared with random trials. This is further evidence that participants use chunking without being explicitly aware they were doing so.

The evidence overall appears to be for a mixture of implicit and explicit awareness of strategy use, but with implicit processes being more common.

7.10 IS WORKING MEMORY TRAINING CLINICALLY USEFUL?

A criticism of cognitive training regimes is that they focus on laboratory based training tools and assessments and may lack ecological validity^{49 180}. A previous meta-analysis has reported limited transfer effects of cognitive training to activities of daily living¹⁸⁷. The current study also found no significant training-related effects on IADLs, however as suggested above, the IADL measure may not have been sensitive to more subtle effects on function. More importantly however, are the training-related improvements that were seen on general cognitive function. The between group difference on the ADAS-Cog score of -3.6 points is near the 4 point criteria for a minimally clinically important change and is of a similar magnitude to reported effects of general cognition seen in pharmacological trials²²⁵. Therefore this study provides support for working memory training providing an equivalent level of general cognitive benefit to currently available therapies.

This study also demonstrated that this type of training is acceptable to participants with AD and their carers. Once training had commenced, no participants dropped out of the study, despite the commitment required, and DEMQOL scores improved in both groups. Anecdotally participants enjoyed engaging with the training and control intervention and felt empowered that they were investing in a potentially useful exercise.

The major barrier to expanding a similar training regime in its current state is the resource implication of using clinical staff to oversee the training. However, similar training could be performed online and independently by participants and carers, with greater freedom of how, where and when they trained.

7.11 LIMITATIONS OF THE STUDY

7.11.1 DIAGNOSTIC DIFFICULTY

This study included individuals at the very early stages of Alzheimer's disease. Effort was made to recruit only participants that clinical services had diagnosed with possible or probable AD, or those at the point of progression from MCI to an AD diagnosis. The differentiation of patients between deteriorating multi-domain MCI and early AD involves skilled clinical assessment, based on the history of functional and cognitive deterioration and progression^{12 13}. Three participants (two training and one control participant) were assessed by their clinical teams to have been at the point of progression from MCI to AD at the time of recruitment. It is acknowledged that patients at this very early stage of AD are likely to overlap with the criteria for MCI. However by primarily considering pre - post intervention performance within the same individuals and analysing within participant performance, any initial heterogeneity in cognitive profile or deterioration was controlled for in the study design.

7.11.2 INCONSISTENCY OF PARTICIPANT AVAILABILITY

Some participants found it difficult to commit to 3 training sessions per week. Therefore some participants had 2 or occasionally only 1 session per week. It was decided that the number of training sessions should remain fixed at 18, rather than insisting on a strict weekly timetable, as this did not appear feasible for many participants. The mean overall time in the study was 73.2 days (SD 21.6) for the control group and 92.7 days (SD 31.07) for the training group. Both groups were positively skewed by one participant in each group who had a longer involvement, and the actual average length of involvement remained within the pre-set 12 weeks, with the difference between groups being non significant (Mann-Whitney U $p=0.077$).

One of the reasons for differences in the length of time some participants were involved in the study was due to periods of no contact. Three participants had breaks in the training of 1-2 weeks due to holidays, illness, and in one case, bereavement. Again it was decided that these individuals would remain in the study and these events would be included in the overall time in the study and frequency of sessions.

7.11.3 INTERRUPTIONS DURING SESSIONS

As all training and assessment sessions were completed in participants' homes there were environmental variables that may have interfered with task performance. Examples included the doorbell or telephone ringing, distraction from a member of the family or event outside, or events that had occurred prior to the session which may have affected energy levels or attention during the sessions. These were impossible to predict or avoid and were only of consequence during timed tasks or those that required an element of sustained attention. On the rare occasion where a timed assessment task was significantly interrupted, the task was repeated. Although the majority of participants were willing to complete most tasks at the time and in the order requested by the researcher, if a participant requested that the baseline or follow up assessment session be terminated early due to tiredness, or due to other time commitments, any remaining tasks were completed at a subsequent session, however this was not a significant issue.

A consequence of allowing a degree of flexibility, for the reasons listed above, was that some of the baseline tasks were completed during the initial 4 training/control sessions, rather than all being completed prior to the first training session. Post assessments were also allowed to be commenced within the last 3 training sessions, providing that these all fell within 2 weeks of the final session. This did not include any of the primary outcome measures which were strictly performed prior to any training session and after the final session had been completed.

7.11.4 BLINDING

A further weakness of the study is that due to one researcher being responsible for conducting all assessments and interventions, it was not possible for outcome assessments to be blinded. This therefore introduces a source of potential bias, despite many of the behavioural assessments being standardised computerised tasks. Therefore future validation of the results in the study would require a randomised double blinded design.

7.11.5 CORRECTING FOR MULTIPLE COMPARISONS

Overall the behavioural primary outcome measures consisted of 4 scores. In addition there were a total of 12 secondary cognitive outcome measures and 3 non cognitive outcome measures (one of

which had 7 sub scores). Therefore there were a total of 19 main outcome measures examined in the study.

The α value of 0.05 should therefore be adjusted for these multiple comparisons to < 0.003 . At this significance level, only the time x group interaction for the ADAS-Cog would remain significant. It could also be argued that the correction for multiple comparisons should include all statistical tests performed on both behavioural and functional imaging data, thus adjusting the level of alpha for all examined results.

It is acknowledged that by not performing a correction for multiple comparisons in this way there is a risk of type 1 errors. However the results reported in the study are consistent with *a priori* hypotheses, and largely consistent within cognitive domains and with previously reported theoretical interpretations. As the study is an fMRI study and also required intensive logistical input from the researcher for the cognitive training (> 600 home visits), it was powered based on previous fMRI and cognitive training studies to detect results at $\alpha = 0.05$ and was also at risk of being under- powered, with a risk of type 2 errors being made. Therefore on balance it was decided to report the significance values as uncorrected for multiple comparisons and acknowledge the risk of error this entails.

7.12 NOVEL CONTRIBUTIONS AND FUTURE DIRECTIONS

The results of this study provide several clear directions for future study.

The investigation of computerised cognitive training to improve cognitive function in early dementia is in its infancy. This study, along with recent findings in healthy older adults²²⁶ and MCI⁴⁶ provides strong support for further investigation of cognitive training. This study makes several important novel contributions.

Firstly, it highlights the importance of focusing cognitive training tools on cognitive functions that remain relatively intact. As has been stated by other authors, cognitive training is likely to be more efficacious if based on improving or attenuating existing skills in the context of early AD⁴⁹. The finding that executive strategy use in working memory is intact in early AD, and can demonstrate improvement with training is evidence for this approach in general and for targeting WM in particular.

Secondly this study provides a specific evidence-based strategic tool for improving working memory and general cognitive function. Chunking training is an effective approach that could easily be adapted into existing cognitive training batteries.

Thirdly, the demonstration of functional plasticity in the WM network following training provides important evidence for the continued ability of the ageing brain to exhibit plasticity, even in the context of early AD. This provides support for the field to actively pursue further evidence for plasticity within AD, conditions that encourage beneficial plasticity, and the underlying processes behind such plasticity at a cellular, synaptic, neural network, functional and cognitive level.

Fourthly, this study provides further evidence for the efficiency theory of cognitive training, and extends these findings to an AD population. It also demonstrates that implicit processes may underpin successful training of higher cognitive processes such as working memory and should encourage future studies to consider both implicit and explicit approaches when designing cognitive training tools.

Fifthly, this study demonstrates that improvement in WM and general cognitive function, and underlying functional plasticity can occur with a relatively low load of training - just 30 minutes of simple chunking training, 2-3 times per week for 18 sessions.

Finally this study provides evidence that computerised cognitive training is both acceptable and enjoyable to an elderly AD population, and therefore is a potential approach to pursue further.

In light of this, the obvious next step is to investigate methods of overcoming the logistical difficulties and increasing access to cognitive training materials in a more flexible way. Online cognitive training would provide such flexibility and would also allow a range of tasks to be performed, by a much larger number of participants, with data collected remotely. This approach has already successfully led to some very large cognitive training studies⁵⁰, and there is an urgent need for open access, evidence based online cognitive training tools, in a growing market of expensive options with limited evidence²²⁷ and an exponentially growing need¹.

Chunking training can easily be incorporated into the existing online battery of Hampshire and Owen (www.cambridgebrainsciences.com) and a follow-on study to examine online training using a tablet interface is planned.

It is also likely that cognitive training is most useful in combination with other strategies. There is increasing evidence that physical exercise in conjunction with cognitive training can improve cognition²²⁸, and there is a need to examine the combination of cognitive training strategies with diet, lifestyle modification, socialisation and pharmacological agents.

As early diagnosis of AD and detection of people at increased risk of developing cognitive impairment and dementia is becoming more urgently required, there is an obvious need to assess whether cognitive training can be used either for primary prevention in healthy elderly people, or secondary prevention in preventing people with MCI from progressing to dementia.

Chunking training may be a useful strategy or adjunct and should therefore be incorporated into future studies of cognitive training in these groups.

This study also raises questions regarding the contribution of meta-cognitive processes in cognitive training, and further studies to investigate metacognition in early AD would be useful in clearly exploring how implicit and explicit processes can be used most efficaciously in cognitive interventions. The extent of impairment of implicit learning in early AD, and the relationship between this and meta-cognition remains unclear, and warrants further study.

7.13 CONCLUSION

This single blinded parallel RCT demonstrated that 18 sessions of chunking training successfully improved verbal WM, episodic memory and general cognitive outcomes. Further, successful cognitive training was associated with functional plasticity in a DLPFC- PPC network, with evidence for increased efficiency in this network following training, and training effects being both explicitly and implicitly mediated.

This study therefore provides evidence for the usefulness and validity of a novel cognitive training regime involving chunking as a therapeutic strategy during the early stages of dementia, and for the ability of the brain to demonstrate functional plasticity even in the context of neurodegeneration.

REFERENCES

1. Prince M, Guerchet M, Prina M. Policy Brief for Heads of Government: The Global Impact of Dementia 2013- 2050. London: Alzheimers Disease International, 2013.
2. Wimo A, Prince M. Alzheimer's Disease International Report 2010: The Global Economic Impact of Dementia, 2010.
3. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006(1):CD005593.
4. WHO. *Dementia: A public health priority*. World Health Organization, 2012.
5. APA. Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5), 2013.
6. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):263-69.
7. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984;34(7):939-44.
8. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* 2004;256(3):240-6.
9. Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, et al. Natural history of mild cognitive impairment in older persons. *Neurology* 2002;59(2):198-205.
10. Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett DA. Mild cognitive impairment: risk of Alzheimer disease and rate of cognitive decline. *Neurology* 2006;67(3):441-5.
11. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med* 2004;256(3):183-94.
12. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National

- Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):270-9.
13. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol* 2007;6(8):734-46.
 14. Tulving E, Thomson DM. Encoding Specificity and Retrieval Processes in Episodic Memory. *Psychol Rev* 1973;80(5):352-73.
 15. Baddeley AD, Hitch G, editors. *Working Memory*. New York: New York: Academic Press, 1974.
 16. Baddeley A. Working memory. *Science* 1992;255(5044):556-9.
 17. Huntley JD, Howard RJ. Working memory in early Alzheimer's disease: a neuropsychological review. *Int J Geriatr Psychiatry* 2010;25(2):121-32.
 18. Collette F, Van der Linden M. Brain imaging of the central executive component of working memory. *Neurosci Biobehav Rev* 2002;26(2):105-25.
 19. Baddeley A. The episodic buffer: a new component of working memory? *Trends Cogn Sci* 2000;4(11):417-23.
 20. Belleville S, Chertkow H, Gauthier S. Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology* 2007;21(4):458-69.
 21. Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease. A critical review. *Brain* 1999;122 (Pt 3):383-404.
 22. Germano C, Kinsella GJ, Storey E, Ong B, Ames D. The episodic buffer and learning in early Alzheimer's disease. *J Clin Exp Neuropsychol* 2008;30(6):627-38.
 23. Miller GA. The magical number seven plus or minus two: some limits on our capacity for processing information. *Psychol Rev* 1956;63(2):81-97.
 24. Bor D, Duncan J, Wiseman RJ, Owen AM. Encoding strategies dissociate prefrontal activity from working memory demand. *Neuron* 2003;37(2):361-7.
 25. Ericsson KA, Chase WG, Faloony S. Acquisition of a memory skill. *Science (New York, N.Y)* 1980;208(4448):1181-2.
 26. Bor D, Cumming N, Scott CE, Owen AM. Prefrontal cortical involvement in verbal encoding strategies. *The European journal of neuroscience* 2004;19(12):3365-70.

27. Bor D, Owen AM. A common prefrontal-parietal network for mnemonic and mathematical recoding strategies within working memory. *Cereb Cortex* 2007;17(4):778-86.
28. Petrides M. Impairments on nonspatial self-ordered and externally ordered working memory tasks after lesions of the mid-dorsal part of the lateral frontal cortex in the monkey. *J Neurosci* 1995;15(1 Pt 1):359-75.
29. Goldman-Rakic PS. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. In: Roberts. AC, Robbins. TW, Weiskrantz. L, editors. *The Prefrontal Cortex: Executive and Cognitive Functions*. Oxford: Oxford University Press, 1998:87- 102.
30. Rao SC, Rainer G, Miller EK. Integration of what and where in the primate prefrontal cortex. *Science (New York, N.Y)* 1997;276(5313):821-4.
31. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annual review of neuroscience* 2001;24:167-202.
32. Logothetis NK. What we can do and what we cannot do with fMRI. *Nature* 2008;453(7197):869-78.
33. Huettel SA, Song AW, McCarthy G. *Functional Magnetic Resonance Imaging*. Second ed. Sunderland, MA: Sinauer Associates, Inc, 2009.
34. The FIL Methods Group. SPM8 manual, 2013.
35. Paulesu E, Frith CD, Frackowiak RS. The neural correlates of the verbal component of working memory. *Nature* 1993;362(6418):342-5.
36. Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, et al. Regional brain activity during working memory tasks. *Brain* 1996;119 (Pt 5):1617-25.
37. Smith EE, Jonides J. Neuroimaging analyses of human working memory. *Proc Natl Acad Sci U S A* 1998;95(20):12061-8.
38. Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. *Cogn Affect Behav Neurosci* 2003;3(4):255-74.
39. Collette F, Salmon E, Van der Linden M, Chicherio C, Belleville S, Degueldre C, et al. Regional brain activity during tasks devoted to the central executive of working memory. *Brain Res Cogn Brain Res* 1999;7(3):411-7.

40. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp* 2005;25(1):46-59.
41. Postle BR, Berger JS, D'Esposito M. Functional neuroanatomical double dissociation of mnemonic and executive control processes contributing to working memory performance. *Proc Natl Acad Sci U S A* 1999;96(22):12959-64.
42. D'Esposito M, Postle BR, Ballard D, Lease J. Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain Cogn* 1999;41(1):66-86.
43. Klingberg T. Concurrent performance of two working memory tasks: potential mechanisms of interference. *Cereb Cortex* 1998;8(7):593-601.
44. Adcock RA, Constable RT, Gore JC, Goldman-Rakic PS. Functional neuroanatomy of executive processes involved in dual-task performance. *Proceedings of the National Academy of Sciences of the United States of America* 2000;97(7):3567-72.
45. Duncan J, Owen AM. Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 2000;23(10):475-83.
46. Belleville S. Cognitive training for persons with mild cognitive impairment. *Int Psychogeriatr* 2008;20(1):57-66.
47. Harris JE. Memory aids people use: Two interview studies. *Memory & Cognition* 1980;8(1):31-38.
48. Turner DC, Robbins TW, Clark L, Aron AR, Dowson J, Sahakian BJ. Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology (Berl)* 2003;165(3):260-9.
49. Sitzler DI, Twamley EW, Jeste DV. Cognitive training in Alzheimer's disease: a meta-analysis of the literature. *Acta Psychiatr Scand* 2006;114(2):75-90.
50. Owen AM, Hampshire A, Grahn JA, Stenton R, Dajani S, Burns AS, et al. Putting brain training to the test. *Nature* 2010;465(7299):775-8.
51. Fernandez A. Brain Training and Cognitive Assessment Market Surpassed \$1.3 Billion In 2013. In: SharpBrains, editor, 2014.
52. Klingberg T. Training and plasticity of working memory. *Trends Cogn Sci* 2010;14(7):317-24.
53. Olesen PJ, Westerberg H, Klingberg T. Increased prefrontal and parietal activity after training of working memory. *Nature neuroscience* 2004;7(1):75-9.

54. McNab F, Varrone A, Farde L, Jucaite A, Bystritsky P, Forssberg H, et al. Changes in cortical dopamine D1 receptor binding associated with cognitive training. *Science* 2009;323(5915):800-2.
55. Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, et al. Effects of cognitive training interventions with older adults: a randomized controlled trial. *JAMA* 2002;288(18):2271-81.
56. Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 2006;296(23):2805-14.
57. Rebok GW, Ball K, Guey LT, Jones RN, Kim HY, King JW, et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. *J Am Geriatr Soc* 2014;62(1):16-24.
58. Verhaeghen P, Marcoen A, Goossens L. Improving memory performance in the aged through mnemonic training: a meta-analytic study. *Psychology and Aging* 1992;7:242-51.
59. Buonomano DV, Merzenich MM. Cortical plasticity: from synapses to maps. *Annu Rev Neurosci* 1998;21:149-86.
60. Jones S, Nyberg L, Sandblom J, Stigsdotter Neely A, Ingvar M, Magnus Petersson K, et al. Cognitive and neural plasticity in aging: general and task-specific limitations. *Neurosci Biobehav Rev* 2006;30(6):864-71.
61. Belleville S, Clement F, Mellah S, Gilbert B, Fontaine F, Gauthier S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain* 2011;134(Pt 6):1623-34.
62. Landau SM, Schumacher EH, Garavan H, Druzgal TJ, D'Esposito M. A functional MRI study of the influence of practice on component processes of working memory. *Neuroimage* 2004;22(1):211-21.
63. Kelly AM, Garavan H. Human functional neuroimaging of brain changes associated with practice. *Cereb Cortex* 2005;15(8):1089-102.
64. McIntosh AR, Rajah MN, Lobaugh NJ. Functional connectivity of the medial temporal lobe relates to learning and awareness. *J Neurosci* 2003;23(16):6520-8.

65. Gould RL, Brown RG, Owen AM, Bullmore ET, Williams SC, Howard RJ. Functional neuroanatomy of successful paired associate learning in Alzheimer's disease. *American Journal of Psychiatry* 2005;162(11):2049-60.
66. Delbeuck X, Van der Linden M, Collette F. Alzheimer's disease as a disconnection syndrome? *Neuropsychol Rev* 2003;13(2):79-92.
67. Collette F, Van der Linden M, Salmon E. Executive dysfunction in Alzheimer's disease. *Cortex* 1999;35(1):57-72.
68. Huntley J, Bor D, Hampshire A, Owen A, Howard R. Working memory task performance and chunking in early Alzheimer's disease. *Br J Psychiatry* 2011;198(5):398-403.
69. Knowlton BJ, Squire LR. The information acquired during artificial grammar learning. *Journal of Experimental Psychology: Learning, Memory, & Cognition* 1994;20(1):79-91.
70. NICE. CG42 Dementia. Supporting people with dementia and their carers in health and social care: National Institute for Health and Care Excellence, 2006 (modified 2012).
71. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98.
72. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *Am J Psychiatry* 1984;141(11):1356-64.
73. Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database Syst Rev* 2012;2:CD005562.
74. Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev* 2013;6:CD003260.
75. Kurz AF, Leucht S, Lautenschlager NT. The clinical significance of cognition-focused interventions for cognitively impaired older adults: a systematic review of randomized controlled trials. *Int Psychogeriatr* 2011;23(9):1364-75.
76. Gould RL, Coulson MC, Howard RJ. Cognitive behavioral therapy for depression in older people: a meta-analysis and meta-regression of randomized controlled trials. *J Am Geriatr Soc* 2012;60(10):1817-30.
77. Clare L, Woods R. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: A review. *Neuropsychological Rehabilitation* 2004;14(4):385-401.

78. Cochrane. www.cochrane.org.
79. Gould RL, Coulson MC, Patel N, Highton-Williamson E, Howard RJ. Interventions for reducing benzodiazepine use in older people: meta-analysis of randomised controlled trials. *Br J Psychiatry* 2014;204(2):98-107.
80. Morris SB. Estimating effect sizes from pretest-posttest-control designs. *Organizational Research Methods* 2008;11:364-86.
81. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to Meta-Analysis: John Wiley & Sons, 2009.
82. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60.
83. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
84. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56(2):455-63.
85. Molnar FJ, Man-Son-Hing M, Fergusson D. Systematic review of measures of clinical significance employed in randomized controlled trials of drugs for dementia. *J Am Geriatr Soc* 2009;57(3):536-46.
86. Howard R, Phillips P, Johnson T, O'Brien J, Sheehan B, Lindesay J, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *Int J Geriatr Psychiatry* 2011;26(8):812-7.
87. Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* 2004;363(9427):2105-15.
88. Burback D, Molnar FJ, St John P, Man-Son-Hing M. Key methodological features of randomized controlled trials of Alzheimer's disease therapy. Minimal clinically important difference, sample size and trial duration. *Dement Geriatr Cogn Disord* 1999;10(6):534-40.
89. Qaseem A, Snow V, Cross JT, Jr., Forciea MA, Hopkins R, Jr., Shekelle P, et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2008;148(5):370-8.

90. PRISMA. www.prisma-statement.org.
91. Galante E, Venturini G, Fiaccadori C. Computer-based cognitive intervention for dementia: preliminary results of a randomized clinical trial. *G Ital Med Lav Ergon* 2007;29(3 Suppl B):B26-32.
92. Heiss WD, Kessler J, Mielke R, Szekely B, Herholz K. Long-term effects of phosphatidylserine, pyritinol, and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation. *Dementia* 1994;5(2):88-98.
93. Jelcic N, Cagnin A, Meneghello F, Turolla A, Ermani M, Dam M. Effects of lexical-semantic treatment on memory in early Alzheimer disease: an observer-blinded randomized controlled trial. *Neurorehabil Neural Repair* 2012;26(8):949-56.
94. Kawashima R, Okita K, Yamazaki R, Tajima N, Yoshida H, Taira M, et al. Reading aloud and arithmetic calculation improve frontal function of people with dementia. *J Gerontol A Biol Sci Med Sci* 2005;60(3):380-4.
95. Baldelli MV, Pirani A, Motta M, Abati E, Mariani E, Manzi V. Effects of reality orientation therapy on elderly patients in the community. *Arch Gerontol Geriatr* 1993;17(3):211-8.
96. Baldelli MV, Boiardi R, Fabbo A, Pradelli JM, Neri M. The role of reality orientation therapy in restorative care of elderly patients with dementia plus stroke in the subacute nursing home setting. *Arch Gerontol Geriatr Suppl* 2002;8:15-22.
97. Bottino CM, Carvalho IA, Alvarez AM, Avila R, Zukauskas PR, Bustamante SE, et al. Cognitive rehabilitation combined with drug treatment in Alzheimer's disease patients: a pilot study. *Clin Rehabil* 2005;19(8):861-9.
98. Breuil V, De Rotrou J, Forette F, Tortrat D, Ganansia-Ganem A, Frambourt A, et al. Cognitive Stimulation of patients with Dementia: Preliminary results. *International Journal of Geriatric Psychiatry* 1994;9:211-17.
99. Buettner LL, Fitzsimmons S, Atav S, Sink K. Cognitive stimulation for apathy in probable early-stage Alzheimer's. *J Aging Res* 2011;2011:480890.
100. Burgener SC, Yang Y, Gilbert R, Marsh-Yant S. The effects of a multimodal intervention on outcomes of persons with early-stage dementia. *Am J Alzheimers Dis Other Dement* 2008;23(4):382-94.

101. Chapman SB, Weiner MF, Rackley A, Hynan LS, Zientz J. Effects of cognitive-communication stimulation for Alzheimer's disease patients treated with donepezil. *J Speech Lang Hear Res* 2004;47(5):1149-63.
102. Coen R, Flynn B, Rigney E, O'Connor E, Fitzgerald I, Murray C, et al. Efficacy of a cognitive stimulation therapy programme for people with dementia. *Irish Journal of Psychological Medicine* 2011;28(3):145-7.
103. Graessel E, Stemmer R, Eichenseer B, Pickel S, Donath C, Kornhuber J, et al. Non-pharmacological, multicomponent group therapy in patients with degenerative dementia: a 12-month randomized, controlled trial. *BMC Med* 2011;9:129.
104. Haight BK, Gibson F, Michel Y. The Northern Ireland life review/life storybook project for people with dementia. *Alzheimers Dement* 2006;2(1):56-8.
105. Luttenberger K, Hofner B, Graessel E. Are the effects of a non-drug multimodal activation therapy of dementia sustainable? Follow-up study 10 months after completion of a randomised controlled trial. *BMC Neurol* 2012;12:151.
106. Onder G, Zanetti O, Giacobini E, Frisoni GB, Bartorelli L, Carbone G, et al. Reality orientation therapy combined with cholinesterase inhibitors in Alzheimer's disease: randomised controlled trial. *Br J Psychiatry* 2005;187:450-5.
107. Onor ML, Trevisiol M, Negro C, Signorini A, Saina M, Aguglia E. Impact of a multimodal rehabilitative intervention on demented patients and their caregivers. *Am J Alzheimers Dis Other Demen* 2007;22(4):261-72.
108. Requena C, Maestu F, Campo P, Fernandez A, Ortiz T. Effects of cholinergic drugs and cognitive training on dementia: 2-year follow-up. *Dement Geriatr Cogn Disord* 2006;22(4):339-45.
109. Spector A, Orrell M, Davies S, Woods B. Can reality orientation be rehabilitated? Development and piloting of an evidence-based programme of cognition-based therapies for people with dementia. *Neuropsychological Rehabilitation* 2001;11(3/4):377-97.
110. Spector A, Thorgrimsen L, Woods B, Royan L, Davies S, Butterworth M, et al. Efficacy of an evidence-based cognitive stimulation therapy programme for people with dementia: randomised controlled trial. *Br J Psychiatry* 2003;183:248-54.

111. Tadaka E, Kanagawa K. Effects of reminiscence group in elderly people with Alzheimer disease and vascular dementia in a community setting. *Geriatr Gerontol Int* 2007;7:167-73.
112. Wang JJ. Group reminiscence therapy for cognitive and affective function of demented elderly in Taiwan. *Int J Geriatr Psychiatry* 2007;22(12):1235-40.
113. Ferrario E, Cappa G, Molaschi M, Rocco M, Fabris F. Reality orientation therapy in institutionalized elderly patients: Preliminary results. *Archives of Gerontology and Geriatrics* 1991;12(Suppl 2):139-42.
114. Lai CK, Chi I, Kayser-Jones J. A randomized controlled trial of a specific reminiscence approach to promote the well-being of nursing home residents with dementia. *Int Psychogeriatr* 2004;16(1):33-49.
115. Avila R, Carvalho IA, Bottino CM, Miotto EC. Neuropsychological rehabilitation in mild and moderate Alzheimer's disease patients. *Behav Neurol* 2007;18(4):225-33.
116. Buschert VC, Friese U, Teipel SJ, Schneider P, Merensky W, Rujescu D, et al. Effects of a newly developed cognitive intervention in amnesic mild cognitive impairment and mild Alzheimer's disease: a pilot study. *J Alzheimers Dis* 2011;25(4):679-94.
117. Davis RN, Massman PJ, Doody RS. Cognitive intervention in Alzheimer disease: a randomized placebo-controlled study. *Alzheimer Dis Assoc Disord* 2001;15(1):1-9.
118. Koltai D, Welsh-Bohmer K, Schmechel D. Influence of anosognosia on treatment outcome among dementia patients. *Neuropsychological Rehabilitation* 2001;11(3/4):455-75.
119. Kurz A, Thone-Otto A, Cramer B, Egert S, Frolich L, Gertz HJ, et al. CORDIAL: cognitive rehabilitation and cognitive-behavioral treatment for early dementia in Alzheimer disease: a multicenter, randomized, controlled trial. *Alzheimer Dis Assoc Disord* 2012;26(3):246-53.
120. Maci T, Pira FL, Quattrocchi G, Nuovo SD, Perciavalle V, Zappia M. Physical and cognitive stimulation in Alzheimer Disease. the GAIA Project: a pilot study. *Am J Alzheimers Dis Other Demen* 2012;27(2):107-13.
121. Niu YX, Tan JP, Guan JQ, Zhang ZQ, Wang LN. Cognitive stimulation therapy in the treatment of neuropsychiatric symptoms in Alzheimer's disease: a randomized controlled trial. *Clin Rehabil* 2010;24(12):1102-11.
122. Quayhagen MP, Quayhagen M, Corbeil RR, Roth PA, Rodgers JA. A dyadic remediation program for care recipients with dementia. *Nurs Res* 1995;44(3):153-9.

123. Tarraga L, Boada M, Modinos G, Espinosa A, Diego S, Morera A, et al. A randomised pilot study to assess the efficacy of an interactive, multimedia tool of cognitive stimulation in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2006;77(10):1116-21.
124. Beck C, Heacock P, Mercer S, Thatcher R, Sparkman C. The impact of cognitive skills remediation training on persons with Alzheimer's disease or mixed dementia. *J Geriatr Psychiatry* 1988;21(1):73-88.
125. Neely AS, Vikstrom S, Josephsson S. Collaborative memory intervention in dementia: caregiver participation matters. *Neuropsychol Rehabil* 2009;19(5):696-715.
126. Schwenk M, Zieschang T, Oster P, Hauer K. Dual-task performances can be improved in patients with dementia: a randomized controlled trial. *Neurology* 2010;74(24):1961-8.
127. Zarit SH, Zarit JM, Reever KE. Memory training for severe memory loss: effects on senile dementia patients and their families. *Gerontologist* 1982;22(4):373-7.
128. Cahn-Weiner DA, Malloy PF, Rebok GW, Ott BR. Results of a randomized placebo-controlled study of memory training for mildly impaired Alzheimer's disease patients. *Appl Neuropsychol* 2003;10(4):215-23.
129. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cogn Psychol* 2000;41(1):49-100.
130. Corsi PM. Human memory and the medial temporal region of the brain. McGill University, 1972.
131. Wechsler D. *Wechsler Memory Scale- Third Edition*. San Antonio, Texas: The Psychological Corporation, 1997.
132. Backman L, Small BJ. Influences of cognitive support on episodic remembering: tracing the process of loss from normal aging to Alzheimer's disease. *Psychol Aging* 1998;13(2):267-76.
133. Osterrieth PA. Le test de copie d'une figure complexe: contribution a l'etude de la perception et la memorie. *Arch Psychol*. 1944;30:286-356.
134. Rey A. *L'examen clinique en psychologie*. Paris, France: Press Universitaire de France, 1964.
135. Benedict RH, Zgaljardic DJ. Practice effects during repeated administrations of memory tests with and without alternate forms. *J Clin Exp Neuropsychol* 1998;20(3):339-52.

136. Benedict RHB, Schretlen D, Groninger L, Dobraski M, Shpritz B. Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity. *Psychological Assessment*, 1996;8:145-53.
137. Lezak MD. *Neuropsychological assessment*. Oxford: Oxford University Press, 1995.
138. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Mot Skills* 1958;8:271-6.
139. Raven J, Raven JC, Court JH. *Manual for Raven's Progressive Matrices and Vocabulary Scales*. San Antonio, TX:: Harcourt Assessment, 2004.
140. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000;55(11):1621-6.
141. Della Sala S, Laiacona M, Spinnler H, Ubezio C. A cancellation test: its reliability in assessing attentional deficits in Alzheimer's disease. *Psychol Med* 1992;22(4):885-901.
142. Serfaty M, Csipke E, Haworth D, Murad S, King M. A talking control for use in evaluating the effectiveness of cognitive-behavioral therapy. *Behav Res Ther* 2011;49(8):433-40.
143. <http://www.randomization.com/>.
144. Nelson HE. *National Adult Reading Test*. Windsor, UK: NFER-Nelson, 1982.
145. Nelson HE, O'Connell A. Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex* 1978;14(2):234-44.
146. Blair J, Spreen O. Predicting premorbid IQ: A revision of the national adult reading test,. *Clinical Neuropsychologist* 1989;3(2):129-36.
147. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey MB, et al. Development and validation of a geriatric depression screening scale: A preliminary report. . *Journal of Psychiatric Research* 1983;17:37-49.
148. Montorio I, Izal M. The Geriatric Depression Scale: a review of its development and utility. *Int Psychogeriatr* 1996;8(1):103-12.
149. Hachinski VC, Iliff LD, Zilhka E, Duboulay GH, Mcallister VL, Marshall J, et al. Cerebral Blood-Flow in Dementia. *Arch Neurol-Chicago* 1975;32(9):632-37.
150. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;44(12):2308-14.

151. Webster DD. Critical analysis of the disability in Parkinson's disease. *Mod Treat* 1968;5(2):257-82.
152. Corsi PM. Human memory and the medial temporal region of the brain. *Dissertation Abstracts International* 1972;34(819B).
153. Carlesimo GA, Fadda L, Lorusso S, Caltagirone C. Verbal and spatial memory spans in Alzheimer's and multi-infarct dementia. *Acta Neurol Scand* 1994;89(2):132-8.
154. Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M, et al. A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain* 1988;111(Pt 3):695-718.
155. Gould RL, Brown RG, Owen AM, Bullmore ET, Williams SC, Howard RJ. Functional neuroanatomy of successful paired associate learning in Alzheimer's disease. *Am J Psychiatry* 2005;162(11):2049-60.
156. Gould RL, Brown RG, Owen AM, ffytche DH, Howard RJ. fMRI BOLD response to increasing task difficulty during successful paired associates learning. *Neuroimage* 2003;20(2):1006-19.
157. Hampshire A, Owen A. www.cambridgebrainsciences.com: MRC Technology.
158. Baddeley AD. A three-minute reasoning test based on grammatical transformation. *Psychometric science* 1968;10:341-42.
159. Owen AM, Morris RG, Sahakian BJ, Polkey CE, Robbins TW. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain* 1996;119 (Pt 5):1597-615.
160. Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* 2006;21(11):1078-85.
161. Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA. Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Arch Clin Neuropsychol* 2008;23(2):129-37.
162. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. 'Oops!': performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. *Neuropsychologia* 1997;35(6):747-58.

163. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* 1969;9(3):179-86.
164. Smith SC, Lamping DL, Banerjee S, Harwood RH, Foley B, Smith P, et al. Development of a new measure of health-related quality of life for people with dementia: DEMQOL. *Psychol Med* 2007;37(5):737-46.
165. Dixon R, Hultsch D, Hertzog C. The Metamemory in Adulthood (MIA) Questionnaire. *Psychopharmacology Bulletin* 1988;24:671-88.
166. Statistical Package for Social Sciences (SPSS) version 22.0 [program]. 22.0 version, 2013.
167. SPM8 www.fil.ion.ucl.ac.uk/spm/software/spm8/ [program]. London.
168. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007;38(1):95-113.
169. TSDiffAna, <http://sourceforge.net/projects/spmtools/> [program].
170. Brett M, Anton JL, Valabregue R, Poline J-B. Region of interest analysis using an SPM toolbox. *8th International Conference on Functional Mapping of the Human Brain*. Sendai, Japan: NeuroImage, 2002.
171. Ashburner J, . VBM Tutorial, www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10, 2010.
172. Friston KJ, Buechel C, Fink GR, Morris J, Rolls E, Dolan RJ. Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 1997;6(3):218-29.
173. O'Reilly JX, Woolrich MW, Behrens TE, Smith SM, Johansen-Berg H. Tools of the trade: psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci* 2012;7(5):604-9.
174. Wechsler D. *Wechsler Memory Scale*. 3rd edn ed: London: The Psychological Corporation, 1998.
175. Lezak MD. *Neuropsychological assessment (3rd ed.)*. New York: Oxford University Press, 1995.
176. Woolgar A, Bor D, Duncan J. Global increase in task-related fronto-parietal activity after focal frontal lobe lesion. *J Cogn Neurosci* 2013;25(9):1542-52.
177. Dahlin E, Neely AS, Larsson A, Backman L, Nyberg L. Transfer of learning after updating training mediated by the striatum. *Science* 2008;320(5882):1510-2.
178. Bor D. *The Ravenous Brain. How the new science of consciousness explains our insatiable search for meaning*. New York, NY: Basic Books, 2012.

179. Baars BJ, Franklin S. How conscious experience and working memory interact. *Trends Cogn Sci* 2003;7(4):166-72.
180. Morrison AB, Chein JM. Does working memory training work? The promise and challenges of enhancing cognition by training working memory. *Psychon Bull Rev* 2011;18(1):46-60.
181. Bor D, Seth AK. Consciousness and the prefrontal parietal network: insights from attention, working memory, and chunking. *Front Psychol* 2012;3:63.
182. Landmann C, Dehaene S, Pappata S, Jobert A, Bottlaender M, Roumenov D, et al. Dynamics of prefrontal and cingulate activity during a reward-based logical deduction task. *Cereb Cortex* 2007;17(4):749-59.
183. Backman L. Utilizing compensatory task conditions for episodic memory in Alzheimer's disease. *Acta Neurol Scand Suppl* 1996;165:109-13.
184. Gathercole SE, Baddeley AD. Phonological Working-Memory - a Critical Building-Block for Reading Development and Vocabulary Acquisition. *Eur J Psychol Educ* 1993;8(3):259-72.
185. Smith EE, Jonides J, Marshuetz C, Koeppel RA. Components of verbal working memory: evidence from neuroimaging. *Proc Natl Acad Sci U S A* 1998;95(3):876-82.
186. Kalpouzos G, Eustache F, de la Sayette V, Viader F, Chetelat G, Desgranges B. Working memory and FDG-PET dissociate early and late onset Alzheimer disease patients. *J Neurol* 2005;252(5):548-58.
187. Clare L, Woods RT, Moniz Cook ED, Orrell M, Spector A. Cognitive rehabilitation and cognitive training for early-stage Alzheimer's disease and vascular dementia. *Cochrane Database Syst Rev* 2003(4):CD003260.
188. Cabeza R, Dolcos F, Graham R, Nyberg L. Similarities and differences in the neural correlates of episodic memory retrieval and working memory. *Neuroimage* 2002;16(2):317-30.
189. Ranganath C, Johnson MK, D'Esposito M. Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia* 2003;41(3):378-89.
190. Horn JL, Cattell RB. Age differences in fluid and crystallized intelligence. *Acta Psychol (Amst)* 1967;26(2):107-29.
191. Kane MJ, Engle RW. The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: an individual-differences perspective. *Psychon Bull Rev* 2002;9(4):637-71.

192. Hampshire A, Highfield RR, Parkin BL, Owen AM. Fractionating human intelligence. *Neuron* 2012;76(6):1225-37.
193. Brehmer Y, Rieckmann A, Bellander M, Westerberg H, Fischer H, Backman L. Neural correlates of training-related working-memory gains in old age. *Neuroimage* 2011;58(4):1110-20.
194. Quayhagen MP, Quayhagen M, Corbeil RR, Hendrix RC, Jackson JE, Snyder L, et al. Coping with dementia: evaluation of four nonpharmacologic interventions. *Int Psychogeriatr* 2000;12(2):249-65.
195. Luck T, Lupp M, Angermeyer MC, Villringer A, König HH, Riedel-Heller SG. Impact of impairment in instrumental activities of daily living and mild cognitive impairment on time to incident dementia: results of the Leipzig Longitudinal Study of the Aged. *Psychol Med* 2011;41(5):1087-97.
196. Reppermund S, Brodaty H, Crawford JD, Kochan NA, Draper B, Slavin MJ, et al. Impairment in instrumental activities of daily living with high cognitive demand is an early marker of mild cognitive impairment: the Sydney Memory and Ageing Study. *Psychol Med* 2013;43(11):2437-45.
197. Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. *Trends Cogn Sci* 2010;14(4):172-9.
198. Petersen SE, van Mier H, Fiez JA, Raichle ME. The effects of practice on the functional anatomy of task performance. *Proc Natl Acad Sci U S A* 1998;95(3):853-60.
199. Duncan J. An adaptive coding model of neural function in prefrontal cortex. *Nat Rev Neurosci* 2001;2(11):820-9.
200. Asaad WF, Rainer G, Miller EK. Neural activity in the primate prefrontal cortex during associative learning. *Neuron* 1998;21(6):1399-407.
201. Debaere F, Wenderoth N, Sunaert S, Van Hecke P, Swinnen SP. Changes in brain activation during the acquisition of a new bimanual coordination task. *Neuropsychologia* 2004;42(7):855-67.
202. Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. *The European journal of neuroscience* 1996;8(4):637-48.

203. Karni A, Meyer G, Jezard P, Adams MM, Turner R, Ungerleider LG. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature* 1995;377(6545):155-8.
204. Poldrack RA. Imaging brain plasticity: conceptual and methodological issues--a theoretical review. *Neuroimage* 2000;12(1):1-13.
205. Kozorovitskiy Y, Gross CG, Kopil C, Battaglia L, McBreen M, Stranahan AM, et al. Experience induces structural and biochemical changes in the adult primate brain. *Proc Natl Acad Sci U S A* 2005;102(48):17478-82.
206. Comeau WL, McDonald RJ, Kolb BE. Learning-induced alterations in prefrontal cortical dendritic morphology. *Behav Brain Res* 2010;214(1):91-101.
207. Zhang W, Linden DJ. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. *Nat Rev Neurosci* 2003;4(11):885-900.
208. Sanes JN, Donoghue JP. Plasticity and primary motor cortex. *Annu Rev Neurosci* 2000;23:393-415.
209. Jansma JM, Ramsey NF, Slagter HA, Kahn RS. Functional anatomical correlates of controlled and automatic processing. *J Cogn Neurosci* 2001;13(6):730-43.
210. Garavan H, Kelley D, Rosen A, Rao SM, Stein EA. Practice-related functional activation changes in a working memory task. *Microsc Res Tech* 2000;51(1):54-63.
211. Buchel C, Coull JT, Friston KJ. The predictive value of changes in effective connectivity for human learning. *Science* 1999;283(5407):1538-41.
212. Hempel A, Giesel FL, Garcia Caraballo NM, Amann M, Meyer H, Wustenberg T, et al. Plasticity of cortical activation related to working memory during training. *Am J Psychiatry* 2004;161(4):745-7.
213. Westerberg H, Klingberg T. Changes in cortical activity after training of working memory--a single-subject analysis. *Physiol Behav* 2007;92(1-2):186-92.
214. Willis SL, Tennstedt SL, Marsiske M, Ball K, Elias J, Koepke KM, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA* 2006;296(23):2805-14.
215. Yang J, Li P. Brain networks of explicit and implicit learning. *PLoS One* 2012;7(8):e42993.
216. Fletcher P, Buchel C, Josephs O, Friston K, Dolan R. Learning-related neuronal responses in prefrontal cortex studied with functional neuroimaging. *Cereb Cortex* 1999;9(2):168-78.

217. Smith JC, Nielson KA, Antuono P, Lyons JA, Hanson RJ, Butts AM, et al. Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. *J Alzheimers Dis* 2013;37(1):197-215.
218. Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, et al. Training-induced functional activation changes in dual-task processing: an fMRI study. *Cereb Cortex* 2007;17(1):192-204.
219. Gaab N, Gaser C, Schlaug G. Improvement-related functional plasticity following pitch memory training. *Neuroimage* 2006;31(1):255-63.
220. Hampstead BM, Stringer AY, Stilla RF, Giddens M, Sathian K. Mnemonic strategy training partially restores hippocampal activity in patients with mild cognitive impairment. *Hippocampus* 2012;22(8):1652-8.
221. van Paasschen J, Clare L, Yuen KS, Woods RT, Evans SJ, Parkinson CH, et al. Cognitive rehabilitation changes memory-related brain activity in people with Alzheimer disease. *Neurorehabil Neural Repair* 2013;27(5):448-59.
222. Rypma B, Berger JS, D'Esposito M. The influence of working-memory demand and subject performance on prefrontal cortical activity. *J Cogn Neurosci* 2002;14(5):721-31.
223. Druzgal TJ, D'Esposito M. Dissecting contributions of prefrontal cortex and fusiform face area to face working memory. *J Cogn Neurosci* 2003;15(6):771-84.
224. Anderson VM, Schott JM, Bartlett JW, Leung KK, Miller DH, Fox NC. Gray matter atrophy rate as a marker of disease progression in AD. *Neurobiol Aging* 2012;33(7):1194-202.
225. Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology* 1998;50(1):136-45.
226. Kueider AM, Parisi JM, Gross AL, Rebok GW. Computerized cognitive training with older adults: a systematic review. *PLoS One* 2012;7(7):e40588.
227. Rabipour S, Raz A. Training the brain: fact and fad in cognitive and behavioral remediation. *Brain Cogn* 2012;79(2):159-79.
228. Dannhauser TM, Cleverley M, Whitfield TJ, Fletcher BC, Stevens T, Walker Z. A complex multimodal activity intervention to reduce the risk of dementia in mild cognitive impairment-

ThinkingFit: pilot and feasibility study for a randomized controlled trial. *BMC Psychiatry* 2014;14(1):129.

APPENDIX 1 - CONSENT FORMS AND INFORMATION SHEETS

BRIEF INFORMATION LEAFLET

**Institute of
Psychiatry**

at The Maudsley

Section of Old Age Psychiatry
Professor Simon Lovestone
Head of Section

MRC Centre for Neurodegeneration Research
King's College London
Institute of Psychiatry
Box P070
De Crespigny Park
Denmark Hill
London SE5 8AF

KING'S
College
LONDON

University of London

VOLUNTEERS NEEDED FOR MEMORY RESEARCH IN ALZHEIMER'S DISEASE

Investigating memory training in early Alzheimer's disease

Alzheimer's disease is a common disease that affects older people. In the early stages of the disease, people often notice difficulties with their memory, however it is not known whether simple training in the use of memory strategies can lead to an improvement in memory.

We are currently looking for volunteers who are at the very early stages of Alzheimer's Disease to take part in our study. We will be investigating whether a simple 6 week memory training program can improve memory. The study has 3 main components:

- 1) Firstly we will be asking volunteers to complete a series of standard questionnaires and memory tests that look at their memory and abilities to do everyday tasks. These questionnaires and tests will be done at the beginning and end of the study.
- 2) Secondly we will be asking volunteers to 'train' their memory three times a week for six weeks. This will require meeting with the researcher at your home for about half an hour on each occasion to practice memory tasks using a computer.
- 3) Finally we will be asking volunteers to have 2 brain scans, one at the beginning and one at the end of the study to look at how memory training affects brain activity. The brain scans will take place at the Institute of Psychiatry, London. (All transport and refreshments will be provided for the volunteer and a friend or relative).

This research is important as it will help our understanding of how memory is affected at the early stages of Alzheimer's disease and assess whether memory training may be a useful treatment.

If you think you might be interested in taking part in this study or if you would like further information then please contact:

Dr Jonathan Huntley
Department of Old Age Psychiatry, Box P070, Institute of Psychiatry, De Crespigny Park
London SE5 8AF
Tel. 020 7848 0508 (office)
Mobile: 07854 451 519
Email: jonathan.huntley@kcl.ac.uk

Many thanks for taking the time to read this leaflet.

V2 (20th Sept 2010)

SHORT CONSENT FORM FOR MEDICAL RECORDS

**Institute of
Psychiatry**

at The Maudsley

Section of Old Age Psychiatry
Professor Simon Lovestone
Head of Section

MRC Centre for Neurodegeneration Research
King's College London
Institute of Psychiatry
Box PO70
De Crespigny Park
Denmark Hill
London SE5 8AF

KING'S
College
LONDON

University of London

Investigating the benefits of memory training using 'chunking' in people with early Alzheimer's Disease

Name of researcher:

Date:

I understand that I will be asked to complete screening questionnaires that will ask questions about my medical history, memory and mood.

☐

I understand that as a result of the screening assessment I may not be eligible to take part in the study.

☐

I understand that Dr Huntley may contact my GP or access my medical records to clarify aspects of my medical history if necessary. I understand my GP will only be informed if any of the results of the investigations carried out as a part of the research are important for my health and this has been discussed with me.

☐

I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting my future medical care or legal rights.

☐

Name of participant
(IN CAPITALS)

Participant's signature Date: Time:.....

Name of researcher
(IN CAPITALS)

Researcher's signature Date:
Time.....

Thank you for helping with this research.

Version 2 (24th September 2010)

FULL CONSENT FORM FOR STUDY

**Institute of
Psychiatry**

at The Maudsley

Section of Old Age Psychiatry
Professor Simon Lovestone
Head of Section

MRC Centre for Neurodegeneration Research
King's College London
Institute of Psychiatry
Box PO70
De Crespigny Park
Denmark Hill
London SE5 8AF

KING'S
College
LONDON

University of London

Investigating the benefits of memory training using 'chunking' in people with early Alzheimer's Disease

Name of researcher:

Date:

I understand that I will be asked to complete screening questionnaires that will ask questions about my medical history, memory and mood.

☐

I understand that as a result of the screening assessment I may not be eligible to take part in the study.

☐

I understand that Dr Huntley may contact my GP or access my medical records to clarify aspects of my medical history if necessary. I understand my GP will only be informed if any of the results of the investigations carried out as a part of the research are important for my health and this has been discussed with me.

☐

I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting my future medical care or legal rights.

☐

I confirm that I have read the Information Sheet on the above project dated 20/09/10 (Version 2) and have been given a copy of the document to keep.

☐

I confirm that I have read the MRI Information Sheet ('your functional MRI scan') dated 13/07/10 (Version 1) and have been given a copy of the document to keep.

☐

I understand that the study involves 21 visits for assessments and memory training and 2 MRI brain scans that will take place at the Institute of Psychiatry.

☐

I understand that my doctor will be informed if any of the results of the investigations carried out as a part of the research are important for my health.

☐

I understand that my participation is voluntary and that I am free to withdraw from the study at any time, without having to give a reason for withdrawing and without affecting my future medical care or legal rights.

☐

I agree to take part in the above study.

☐

Name of participant
(IN CAPITALS)

Participant's signature Date: Time.....

The researcher has explained why the research is being carried out and has answered the participant's questions about the study.

Name of researcher

(IN CAPITALS)

Researcher's signature Date:
Time.....

Thank you for helping with this research.

Version 2 (24th September 2010)

INFORMATION SHEET FOR PARTICIPANT

**Institute of
Psychiatry**

at The Maudsley

Section of Old Age Psychiatry
Professor Simon Lovestone
Head of Section

MRC Centre for Neurodegeneration Research
King's College London
Institute of Psychiatry
Box PO70
De Crespigny Park
Denmark Hill
London SE5 8AF

KING'S
College
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University of London

Participant Information Sheet

Investigating memory training in early Alzheimer's Disease

Version 2 (20th September 2010)

You are being invited to take part in a research study. Before you make a decision, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information carefully and discuss it with your relatives, friends or GP if you wish. Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

What is the purpose of the study?

It is unclear whether memory training leads to a general improvement in memory, particularly in people with Alzheimer's Disease. 'Chunking' is a strategy that can help us remember things, by breaking information up into 'chunks'. An example of this is how we remember telephone numbers. We find it easier to remember: 0207 848 0346, than a list of 11 separate numbers. There is some evidence that people at the very early stage of Alzheimer's disease can use chunking as a strategy to help their memory. We are therefore going to study whether a 6 week period of memory training by either learning chunking techniques or practicing memory games leads to an improvement in memory. Using brain scans we will also look at whether this memory training will lead to changes in brain activity.

The aim is to learn more about whether memory training may be a useful treatment for Alzheimer's disease.

Why have I been chosen?

We are asking 30 people at the very early stages of Alzheimer's disease to take part in the study. You have been approached because you have expressed some interest in the study.

Do I have to take part?

It is up to you to decide whether or not you want to take part. If you decide to take part you are free to withdraw at any time and without having to give a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive or your legal rights.

If you decide to take part then you will be asked to sign a consent form and given a copy of this.

What will happen to me if I take part?

The study has 3 main parts:

1) INITIAL SCREENING AND ASSESSMENTS:

You will be asked for your consent to take part in this initial screening interview and it is possible that following this you or the researcher may decide that you are not suitable for the study. You will be

asked to take part in an interview that will last approximately one hour. In this interview you will be asked questions about yourself and will be asked to take part in some standard psychological tests. These will be done to assess whether you are eligible to take part in the study.

If you are eligible and wish to take part in the study, we will then arrange a second appointment to complete further questionnaires and memory tests. These will ask more detailed questions about your memory and how you manage everyday tasks. You will also be shown and asked to complete 2 memory tests on a computer. In one task you will be shown a sequence of numbers, which you will be asked to hold in your memory and then repeat back to the researcher. In the other task you will be shown a pattern of squares on the screen and then be asked to remember and immediately recall the pattern by pressing on the computer screen. These tasks will form the basis of the period of memory training and also be the tests you will be asked to do whilst undergoing brain scans. This appointment will last approximately two hours.

After the memory training period we will arrange a final assessment session, where the same memory tests will be done, to see if there has been any change

2) MEMORY TRAINING

The memory training programme will take a total of 6 weeks. It will be quite intensive and require you to meet with the researcher (Dr Huntley) for one hour, three times per week for 6 weeks. Each meeting will be arranged at your convenience in advance and all meetings could take place in your home if that is convenient or at the Institute of Psychiatry if you would prefer.

We will be comparing 2 types of memory training in the study. In one type of training, volunteers will be taught how to use 'chunking' to improve memory, as described above. In the other type of training volunteers will practice simpler memory tests. In order to make sure we can accurately compare these two types of training, all volunteers will be allocated to one group or the other randomly. We do not yet know if either of these types of memory training are effective and it is important that we are able to compare them to each other, which is why volunteers will be allocated to the groups by chance.

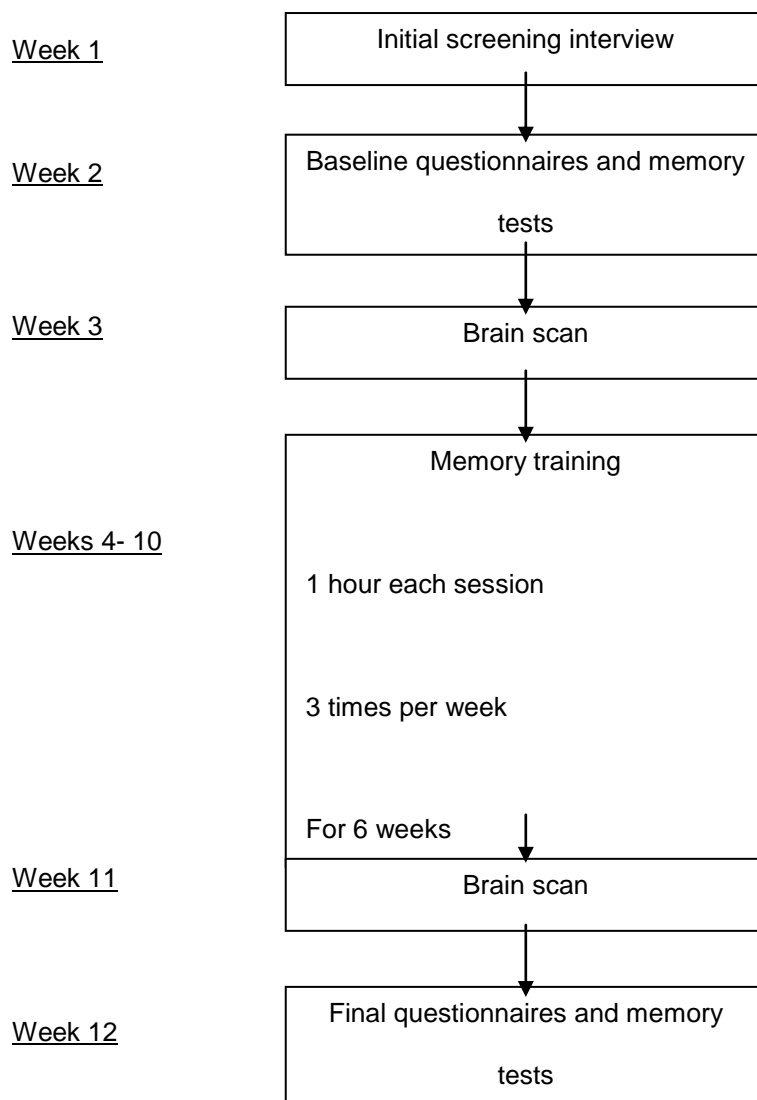
3) BRAIN SCANS

Each volunteer will have a brain scan before and after the 6 week memory training period. A technique called functional magnetic resonance imaging (fMRI) will be used. Functional MRI is a non-invasive imaging technique for taking pictures of the brain and has no known side-effects. The procedure does not involve any injections or X-rays. Using functional MRI, we are able to learn about how the brain works by looking at the blood flow to different parts of the brain whilst the brain performs different memory tasks. Volunteers will be asked to do the memory task involving remembering a list of 4 numbers during the scan, so we can see if memory training has had an effect on brain activity. The brain scans will take place at the Institute of Psychiatry, London. Transport for you and a friend or relative will be provided to travel to and from the Institute of Psychiatry on 2 occasions for the scans.

Please see the separate 'your functional MRI scan' leaflet for further information on having a brain scan.

There is no payment for the study, however all transport will be provided or travel expenses reimbursed. All participants in the study will also be entered into a draw to win a £50 voucher.

Summary of what the study involves:



There will therefore be a total of 23 visits over approximately 12 weeks

What are the possible disadvantages and risks of taking part?

There are no known risks or side-effects associated with carrying out the questionnaires or computerized tasks. You may feel anxious before or tired after taking part in the tasks, but we will do everything we can to prevent this. You will be asked about your well-being at all times, and you will be given the opportunity to have either a short rest break or for the testing or training to be stopped if necessary.

There are no known risks involved in undergoing an fMRI scan. No radiation or injections are involved and you will not feel anything during the scan, however you would be required to lie still for approximately an hour. The MRI scans can be noisy and will not be ideal for anyone who suffers from claustrophobia, as you will be required to lie in a relatively small space. There is a possibility you may feel anxious or tired after taking part, but again we will do everything we can to prevent this. The scans will take place at the Institute of Psychiatry and therefore require you to travel there with a friend or relative on two occasions. All transport and refreshments on the day will be provided. You may find the travel to and from the Institute of Psychiatry tiring or inconvenient, however the timing of these visits will be arranged when convenient for you and by providing all transport by taxis we will aim to reduce any inconvenience as much as possible.

What are the possible benefits of taking part?

The study is designed to investigate whether memory training can improve memory in people at the early stages of Alzheimer's disease. There is therefore a possibility that your memory may benefit from the intervention. However there is no current evidence for this and there may be no benefits from this type of memory training. We hope that the research might lead to new understanding of how memory is affected at the early stages of Alzheimer's disease and ways that it might be improved.

What if something goes wrong?

In the unlikely event that you are harmed due to our negligence or if you have a complaint or any concerns about any aspect of the way you have been approached or treated during the course of this study then please don't hesitate to raise this with us or contact us at the addresses below:

Dr. Jonathan Huntley

Section of Old Age Psychiatry, Box P070, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, Tel: 020 7848 0508 (office)

Professor Robert Howard, Section of Old Age Psychiatry, Box P070, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, Tel: 020 7848 0508 (office).

If you have a complaint and are under the care of the South London and Maudsley Foundation Trust (for example you attend a memory clinic or outpatient community mental health service) and wish to speak to an independent person please contact the Patient Advice and Liaison service (PALS) on 0800 731 2864

Alternatively you can contact the KCL Research Ethics Office (contact details below) who will re-direct your complaint as appropriate.

Contact details for KCL Research Ethics Office: Research Ethics Office, King's College London, Room 7.21 James Clerk Maxwell Building, 57 Waterloo Road, London SE1 8WA.

Email: rec@kcl.ac.uk

The design, management and conduct of the study is covered by the Kings College London Professional indemnity scheme for clinical studies and NHS indemnity scheme.

Will my taking part in this study be kept confidential?

All information collected about you during the course of the research will be kept strictly confidential. All information we collect is only seen by members of the research team. Any research data that is collected will be assigned a unique identification number, and personal information will be removed so that you cannot be recognized from your data. If you withdraw your consent at any time, your data will no longer be used in the study. If you consent to take part in the study then Dr Jonathan Huntley may ask for your permission to inspect your medical records in order to ensure you are eligible for the study, but if this is necessary your permission will be sought for this explicitly.

Will my doctor be informed?

With your permission we will let your GP know you are participating in the study. We will not pass any other information to your doctor unless it is important for your health and you have agreed that we do so.

What will happen to the results of the research study?

When we have collected all the results for this study we will analyse them and then publish and present the results. We will send you a summary of the research findings. You will not be identified in any publication or presentation.

Who has reviewed the study?

This study is being funded by the Medical Research Council. The ethics of the study have been reviewed by the Cambridgeshire 1 Research Ethics Committee.

Contact for Further Information

If you have any questions or require any further information about this study then please do not hesitate to contact:

Dr. Jonathan Huntley,
Section of Old Age Psychiatry, Box P070, Institute of Psychiatry, De Crespigny Park, London SE5
8AF, Tel: 020 7848 0508 (office)

We are very grateful to you for considering taking part in this study.

Version 2 (20th September 2010)

INFORMATION SHEET FOR PARTICIPANT'S GP

**Institute of
Psychiatry**

at The Maudsley

Section of Old Age Psychiatry
Professor Simon Lovestone
Head of Section

MRC Centre for Neurodegeneration Research
King's College London
Institute of Psychiatry
Box PO70
De Crespigny Park
Denmark Hill
London SE5 8AF

KING'S
College
LONDON

University of London

Information Sheet for GP

Investigating the benefits of memory training using 'chunking' in people with early Alzheimer's Disease

Your patient xxxxxxxx has been invited to take part in a research study investigating whether memory training using chunking, a mnemonic strategy, may be a useful treatment for Alzheimer's disease.

What does the study involve?

The study has 3 main parts:

- 1) Firstly volunteers will complete a series of standard questionnaires and memory tests that examine their memory and abilities to do everyday tasks. These questionnaires and tests will be done at the beginning and end of the study.
- 2) Secondly we will be asking volunteers to 'train' their memory three times a week for six weeks, to learn and practice chunking strategies. This will require meeting with the researcher for an hour on each occasion to practice memory tasks using a computer.
- 3) Finally we will be asking volunteers to have 2 fMRI brain scans, one at the beginning and one at the end of the study to look at how memory training affects brain activity.

Why has my patient been chosen?

We are asking 30 people at the early stages of Alzheimer's disease to take part in the study. Your patient has been approached because they have expressed some interest in the study. It is up to your patient to decide whether or not they want to take part and they will be asked to provide informed consent. If they do decide to take part they are free to withdraw at any time and without having to give a reason.

What are the possible disadvantages and risks of taking part?

There are no known risks or side-effects associated with carrying out the questionnaires or computerized tasks or undergoing an fMRI scan. Your patient may feel anxious before or tired after taking part in the tasks, but we will do everything we can to prevent this.

What are the possible benefits of taking part?

The study is designed to investigate whether memory training can improve memory in people at the early stages of Alzheimer's disease. There is therefore a possibility that your patient's memory may benefit from the intervention. However there is no current evidence for this and there may be no benefits from this type of memory training. We hope that the research might lead to new

understanding of how memory is affected at the early stages of Alzheimer's disease and ways that it might be improved.

Who has reviewed the study?

This study is being funded by the Medical Research Council. The ethics of the study have been reviewed by the Cambridgeshire 1 Research Ethics Committee.

If you have any questions or require any further information about this study or if you have any concerns about any aspect of the way your patient has been approached or treated during the course of this study then please contact:

Dr. Jonathan Huntley
Section of Old Age Psychiatry, Box P070, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, Tel: 020 7848 0346 (office)

We are very grateful to your patient for considering taking part in this study.

Version 2 (20th September 2010)

APPENDIX 2 - FMRI QUALITY AND BEHAVIOURAL TABLES

FMRI BEHAVIOURAL DESCRIPTIONS

Subjects who had a reduced number of trials are as follows:

TRAINING GROUP

- 1) CH06A- Only 1 functional run, therefore only 20 trials.
- 2) CH06B- Only 2 functional runs, therefore only 40 trials.
- 3) CH24A- Only 2 functional runs, therefore only 40 trials.
- 4) CH30B- run 3: No response to trials 52-60, therefore deleted blank images: 162-299

CONTROL GROUP

- 1) CH02B: RUN 1 stopped after trial 12, RUN 2 stopped after trial 16, RUN 3: stopped after trial 16, all due to subject stating he saw double. Therefore 44 attempted trials included in imaging analysis.
- 2) CH04A: RUN 2 stopped after 14 trials, therefore 54 attempted trials included in analysis
- 3) CH04B: RUN 3 stopped after 18 trials, therefore 58 attempted trials included in analysis
- 4) CH20B: RUN 3 stopped after 12 trials, therefore 52 attempted trials included in analysis
- 5) CH23A- Only 2 spans (40 trials in total)
- 6) CH23B- Only 2 spans (40 trials in total)

Details on quality of data as assessed by the time series difference analysis (TSDiffANA) toolbox, number of functional runs, behavioural notes, additional movement regressors added to model, number of trials and correct and confident responses for each subject are shown in Table 0-1.

PARTICIPANT	TS DIFFANA VARIANCE NOTES	EXPERIMENTAL SUBJECTS				CONFIDENCE
		BEHAVE NOTES DELETED IMAGES	EXTRA MOVEMENT REGRESSOR	PARAMETERS UNIQUE	TRIALS	
CH05A	OK	N/A	NO	ALL UNIQUE	30 RAND (10 IN 20 COR) 30 STR (10 INC 20 COR)	CONF 24 N/R 5 NOT CONF 31
CH05B	OK	N/A	NO	RUN 1: not conf and incorrect trials non unique	30 RAND (11 IN 19 COR) 30 STR (1 INC 29 COR)	CONF 43 N/R 0 NOT CONF 17
CH06A	OK	ONLY 1 RUN	NO	RUN 1 no notconf trials	10 RAND (1 IN 9 COR) 10 STR (0 IN 10 COR)	CONF 19 N/R 1
CH06B	RUN 1- one variance spike to 400 on graphs 2 and 4, otherwise ok	ONLY 2 RUNS	NO	both runs, no notconf trials	20 RAND (4 IN 16 COR) 20 STR (1 IN 19 COR)	CONF 35 N/R 5
CH09A	OK	N/A	NO	NO NOTCONF TRIALS	30 RAND (2 IN 28 COR) 30 STR (2 INC 28 COR)	CONF- 60
CH09B	OK	NONE	NO	RUN 1 no incorrect trials	30 RAND (2 IN 28 COR) 30 STR (1 IN 29 COR)	CONF 55 NOT CONF 4 BLANK 1
CH10A	RUN 2- variance spikes to 600 at image 1,2,3 RUN 3- one spike to 500 around image 240	NONE	1 (RUN 2, IM 2)	RUN 2 no notconf trials	30 RAND (9 IN 21 COR) 30 STR (6 IN 24 COR)	CONF 57 NOT CONF 3
CH10B	RUN 1- variance spike to 500 around image 240	NONE	1 (RUN 1 IM 241)	RUN 1 AND 2 no notconf trials:	30 RAND (10 IN 20 COR) 30 STR (8 IN 22 COR)	CONF 58 N/R 1 NOT CONF 1
CH11A	RUN 1- 3 variance spikes to 600 around image 190 RUN 2- variance spike to 1200 around	Answered early either in encoding or delay in all trials apart from 14,21,22,41,42,44 ,45	1 (RUN 2 IM 216)	NO CONF RESPONSE	30 RAND (7 IN 23 COR) 30 STR (6 IN 24 COR)	CONF 0 N/R 60

	image 216					
CH11B	RUN 1-variance spike to 1000 around image 80 RUN 3- variance spike to 1000	repeated early in maintenance then again in response in all trials except trial 21	1 (RUN 1, IMAGE 81)	NO CONF RESPONSES	30 RAND (4 IN 26 COR) 30 STR (1 IN 29 COR)	CONF 0 N/R 60
CH14A	RUN 1- variance spike to 1200 around image 124	N/A	2 (RUN 1 IM 124 AND 128)	ALL UNIQUE	30 RAND (7 IN 23 COR) 30 STR (8 IN 22 COR)	CONF 53 N/R 0 NOT CONF 7
CH14B	OK	N/A	NO	ALL UNIQUE	30 RAND (11 IN 19 COR) 30 STR (15 IN 15 COR)	CONF 54 NOT CONF 6
CH15A	OK	N/A	NO	ALL UNIQUE	30 RAND (3 IN 27 COR) 30 STR (3 IN 27 COR)	CONF 44 NOT CONF 15 BLANK 1
CH15B	OK	N/A	NO	NO NOTCONF TRIALS	30 RAND (1 IN 29 CORR) 30 STR (2 IN 28 CORR)	CONF 60
CH16A	OK	N/A	NO	ALL UNIQUE	30 RAND (17 IN 13 COR) 30 STR (16 IN 14 COR)	CONF 30 NOT CONF 30
CH16B	OK	Spoke early in trials 4,7,10,11,28,35,4 6,48,51,56	NO	ALL UNIQUE	30 RAND (14 IN 16 COR) 30 STR (18 IN 12 COR)	CONF 32 N/R 11 NOT CONF 17
CH18A	OK	N/A	NO	ALL UNIQUE	30 RAND (4 IN 26 COR) 30 STR (6 IN (24 COR)	CONF 45 NOT CONF 15
CH18B	OK	N/A	NO	RUN 3: NO INCORRECT TRIALS	30 RAND (3 IN 27 COR) 30 STR (1 IN 29 COR)	CONF 45 NOT CONF 15
CH22A	OK	N/A	NO	RUN 1: no notconf trials RUN 2 no notconf or incorrect trials	30 RAND (4 IN 26 COR) 30 STR (3 IN 27 COR)	CONF 50 N/R 9 NOT CONF 1

CH22B	OK	Spoke early in trials 12,40 ,57	NO	ALL UNIQUE	30 RAND (12 IN 18 COR) 30 STR (12 IN 18 COR)	CONF 40 N/R 1 NOT CONF 19
CH24A	OK	ONLY 2 RUNS Spoke early in trials: 1-16, 24, 28-30, 33-35, 37, 39, 40.	None	NO NOT CONF TRIALS	20 RAND (4 IN 16 CORR) 20 STR (7 IN 13 CORR)	CONF 40 N/R 1 BLANK 19
CH24B	OK	SPOKE EARLY IN TRIALS 2, 29, 42	NO	NO NOTCONF TRIALS	30 RAND (5 IN 25 COR) 30 STR (5 IN 25 COR)	CONF 49 N/R 11
CH27A	RUN 1- one variance spike to 500 around image 298-300 RUN 3 –variance spikes to 3000 around 195, 230 and 298	N/A	10 (RUN 3 : 10 EXTRA 194,196,197,230, 231,232,255,257, 299,300)	ALL UNIQUE	30 RAND (25 IN 5 COR) 30 STR (22 IN 8 COR)	CONF 41 N/R 6 NOT CONF 13
CH27B	RUN 3- variance spike to 700 around images 295, 296	spoke early on trials 3,8,30,32	2 (RUN 3 IM 295,296)	ALL UNIQUE	30 RAND (24 IN 6 COR) 30 STR (16 IN 14 COR)	CONF 44 N/R 2 NOT CONF 14
CH28A	OK	spoke early on trials 4,23,31,38,47,49, 60	NO	ALL UNIQUE	30 RAND (17 IN 13 COR) 30 STR (17 IN 13 COR)	CONF 38 N/R 1 NOT CONF 21
CH28B	OK		NO	ALL UNIQUE	30 RAND (14 IN 16 COR) 30 STR (8 IN 22 COR)	CONF 45 N/R 1 NOT CONF 14
CH29A	OK		NO	RUN 1: no incorrect trials RUN 2 no notconf TRIALS RUN 3: no notconf or incorrect trials	30 RAND (1 IN 29 COR) 30 STR (0 IN 30 COR)	CONF 58 NOT CONF 2
CH29B	OK		NO	NO NOTCONF OR INCORRECT TRIALS	30 RAND (0 IN 30 CORR) 30 STR (0 IN 30 COR)	CONF 60

CH30A	OK	NONE	NO	ALL UNIQUE	30 RAND (11 IN 19 COR) 30 STR (8 IN 22 COR)	CONF 31 N/R 4 NOT CONF 25
CH30B	OK	No response trials 52-60 all images blank after 161 therefore deleted 162-299	NO	ALL UNIQUE	25 RAND (8 IN 17 COR) 26 STR (6 IN 20 COR)	CONF 34 N/R 2 NOT CONF 15
CONTROL SUBJECTS						
CH01A	OK	CONF RESPONSE USED BUTTON BOX	None	RUN 3 : NO NOTCONF RESPONSE	30 RAND (19IN,11COR) 30 STR (10 IN, 20 COR)	CONF 12 N/R 38 NOT CONF 4 BLANK 6
CH01B	RUN 2- variance spike at 1200 at around 290	N/A	2 (RUN 2 IM 292 AND 293	ALL UNIQUE	30 RAND (19 IN 11 COR) 30 STR (18IN, 12 COR)	CONF 19 N/R 9 NOT CONF 31
CH02A	OK	N/A (CONF USED BUTTON BOX)	NONE	ALL UNIQUE	30 RAND (1 IN, 29 COR) 30 STR (5 IN, 25 COR)	CONF 47 N/R 4 NOT CONF 9
CH02B	OK	Difficulty seeing numbers Only 44 attempted trials included in imaging analysis	NONE	ALL UNIQUE	22 RAND (7 IN,15 COR) 22 STR (9 IN, 13 COR)	CONF 25 N/R 26 NOT CONF 9
CH04A	OK	RUN 2 –stopped after 14 trials, therefore only 54 trials included.	NONE	ALL UNIQUE	27 RAND (12 IN,15 COR) 27 STR (9 IN, 18 COR)	CONF 29 N/R- 13 NOT CONF 11 BLANK 7
CH04B	OK	RUN 3 – stopped after 18 trials, therefore only 58 trials included	NONE	ALL UNIQUE	29 RAND (15 IN,14 COR) 29 STR (8 IN, 21 COR)	CONF 44 NOT CONF 11 BLANK 5

CH07A	OK		NONE	ALL UNIQUE	30 RAND (24 IN 6 COR) 30 STR (19 IN 11 COR)	CONF 31 N/R 8 NOTCONF 21
CH07B	RUN 1- variance spike to 600 around image 70	Spoke early in trials 29,55,56	1 (RUN 1 IM 70)	ALL UNIQUE	30 RAND (13 IN,17 COR) 30 STR (12 IN, 18 COR)	CONF 36 N/R 3 NOT CON 21
CH08A	RUN 3- one variance spike to 500 around image 180.	Spoke early in trials 10,50	NO	ALL UNIQUE	30 RAND (8 IN, 22 COR) 30 STR (6 IN, 24 COR)	CONF 56 NOT CONF 4
CH08B	RUN 3- variance spike to 500		NO	NO NOTCONF TRIALS	30 RAND (4 IN, 26 COR) 30 STR (3 IN, 27 COR)	CONF 59 N/R 1
CH12A	OK		NO	ALL UNIQUE	30 RAND (12 IN 18 COR) 30 STR (12 IN, 18 COR)	CONF 44 N/R 1 NOT CONF 15
CH12B	OK	Spoke early in one trial (58) then repeated	NO	ALL UNIQUE	30 RAND (12 IN,28 COR) 30 STR (9 IN, 21 COR)	CONF 51 NOT CONF 9
CH13A	RUN 1- variance spike to 800 around image 160	Spoke early in trials (once in delay) 2,3,5,6,7,10,13, 16,18,19,20,22, 24, 26,27,32,34,35, 36,38,44,45,47, 51, 53,54,56,58,60	NO	ALL UNIQUE	30 RAND (14 IN,16 COR) 30 STR (9 IN, 21 COR)	CONF 35 N/R 13 NOT CONF 12
CH13B	RUN 2- one variance spike to 500 around image 158	Spoke once during delay in trials 8,9, 13,18,19,29,34, 37,38,39,40,43, 51,53	NO	ALL UNIQUE	30 RAND (10 IN,20 COR) 30 STR (12 IN, 18 COR)	CONF 47 N/R 4 NOT CON 8 BLANK 1
CH19A	RUN 1- slice by slice variance one spike of 700 around image 212		NO	No incorrect trials in RUN 1 and 2.	30 RAND (1 IN, 29 COR) 30 STR (0 IN, 30 COR)	CONF 57 N/R 0 NOT CONF 3
CH19B	OK		NO	No unique incorrect	30 RAND (1 IN, 29 COR)	CONF 58

				and not conf trials in run 1, no incorrect trials in runs 2 and 3.	30 STR (1 IN, 29 COR)	N/R 0 NOT CONF 2
CH20A	OK		NO	ALL UNIQUE	30 RAND (11IN, 19 COR) 30 STR (8 IN, 22 COR)	CONF 49 N/R 2 NOT CONF 9
CH20B	RUN 1- max variance to 800 RUN 3 –variance spike around 113	RUN 3 stopped after trial 12, therefore 52 trials included in analysis	4 (RUN 1, IM 12,97,154 RUN 3, IM)	Run 1, no not conf trials. Run 2 no unique incorrect or not conf trials	26 RAND (4 IN, 22 COR) 26 STR (2 IN, 24 COR)	CONF 50 N/R 1 NOT CONF 1 BLANK 8
CH23A	RUN 1- variance spike to 700 around image 280	Only 2 Runs	None	ALL UNIQUE	20 RAND (5 IN, 15 COR) 20 STR (4 IN, 16 COR)	CONF 33 NOT CONF 7 BLANK 20
CH23B	RUN 1 – variance spike to 900 around image 299	Only 2 runs	RUN 1- images 294 and 299	RUN 2 – incorrect and not conf trials not unique	20 RAND (5 IN, 15 COR) 20 STR (2 IN, 18 COR)	CONF 34 NOT CONF 6 BLANK 20
CH25A	RUN 1 – spike to 800 at image 152-155 RUN 2- spike to 700 RUN 3- spike to 1000		NO	ALL UNIQUE	0 RAND (13 IN, 17 COR) 30 STR (15 IN, 15 COR)	CONF 36 N/R 11 NOT CONF 13
CH25B	RUN 1 – spike to 700 RUN 2- spike to 600		NO	ALL UNIQUE	30 RAND (10 INC,20 CORR) 30 STR (6 INC, 24 CORR)	CONF 31 N/R 15 NOT CONF 14
CH26A	OK		NO	ALL UNIQUE	30 RAND (17 IN,13 COR) 30 STR (22 IN, 8 COR)	CONF 24 N/R 3 NOT CONF 33
CH26B	OK		NO	ALL UNIQUE	30 RAND (19 IN,11 COR) 30 CORR (24 IN, 6 COR)	CONF 41 N/R 2 NOT CONF 17
CH31A	OK	NO MPRAGE STRUCTURAL IMAGE		ALL UNIQUE	30 RAND (7 IN, 23 COR) 30 STR (6 INC, 24 COR)	CONF 42 NOT CONF 18
CH31B	RUN 1, one spike to 700 around image 220	NO MPRAGE STRUCTURAL IMAGE		ALL UNIQUE	30 RAND (6 IN, 24 COR) 30 STR (9 IN, 21 COR)	CONF 45 N/R 2 NOT CONF 13

CH32A	OK		NO	RUN 2 no notconf trials RUN 3 not conf and incorrect trials not unique	30 RAND (3 IN, 27 COR) 30 STR (2 IN, 28 COR)	CONF 59 N/R 0 NOT CONF 1
CH32B	RUN 2- variance spike to 800 around image 127		2 (RUN 2 IM 127, 129)	RUN 1 no incorrect and notconf trials	30 RAND (2 IN, 28 COR) 30 STR (0 INC, 30 COR)	CONF 59 NOT CONF 1
CH33A	OK	Spoke early trials 15,17,22,29,37, 48	NO	RUN 2 no unique incorrect and notconf trials	30 RAND (6 IN, 24 COR) 30 STR (4 IN, 26 COR)	CONF 41 N/R 9 NOT CONF 10
CH33B	OK	Spoke early on trials 7,32,41,56	NO	RUN 1 no unique incorrect/notconf trials RUN 2 no incorrect trials	30 RAND (2 IN, 28 COR) 30 STR (2 IN, 28 COR)	CONF 54 NOT CONF 6

Table 0-1: Table of fMRI performance and quality of data

RUN = Each fMRI session had 3 functional runs. IM = image. RAND = random trial. STR = structured trials.

IN = incorrect. COR = correct, CONF = confident response, N/R = no response, NOT CONF = not confident response.

EXAMPLE OF MODELLING MOVEMENT ARTEFACT AS REGRESSOR OF NO INTEREST.

The example below is of subject CH14A who demonstrated a movement spike around images 123-128 during the first span session. This is seen as a spike in z translation and pitch rotation on the image realignment output graphs and also as a spike in slice by slice and scaled variance at the corresponding images. Checking the images revealed artefact present on images 123-128.

The design matrix therefore involved an additional two regressors after the 6 movement regressors in span 1, corresponding to images 124 and 128, where the amount of movement exceeded the stated maximums allowed.

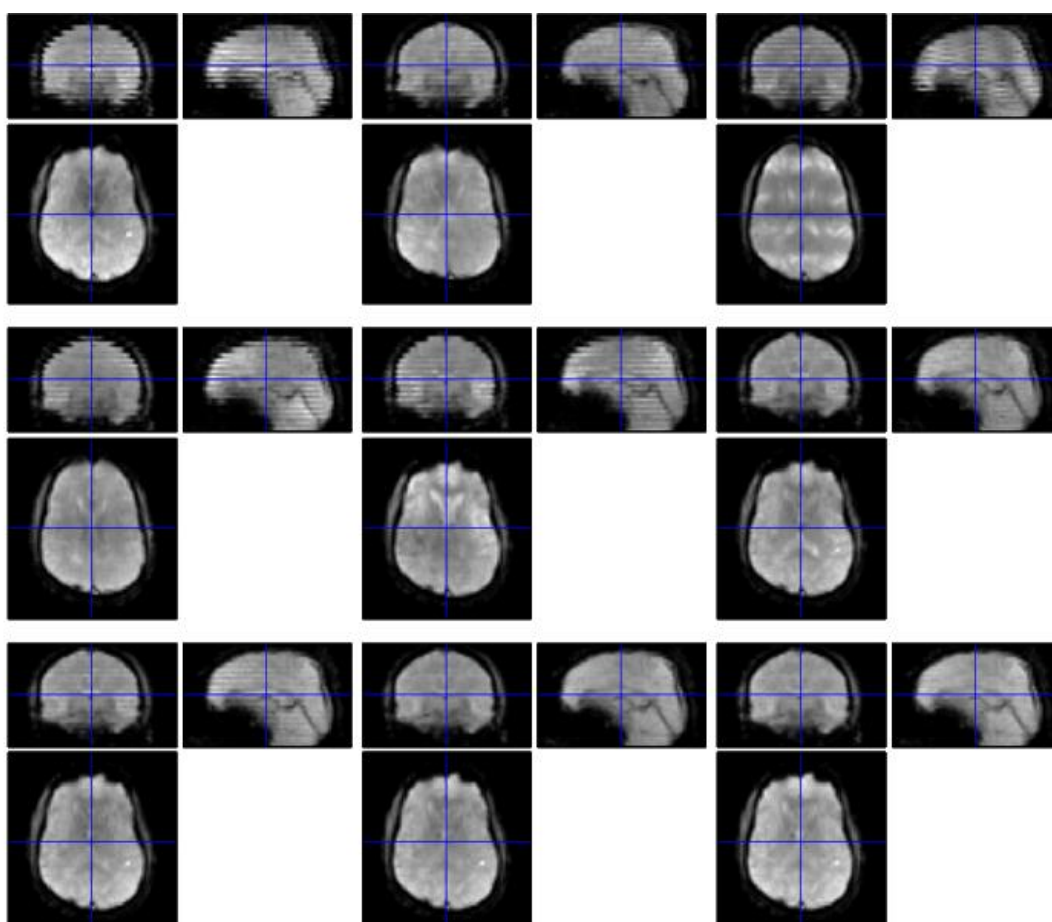


Figure 0-1: Preprocessed functional images 123- 131 from subject CH14A Run 1, demonstrating artefact on images 123-128 as a result of movement.

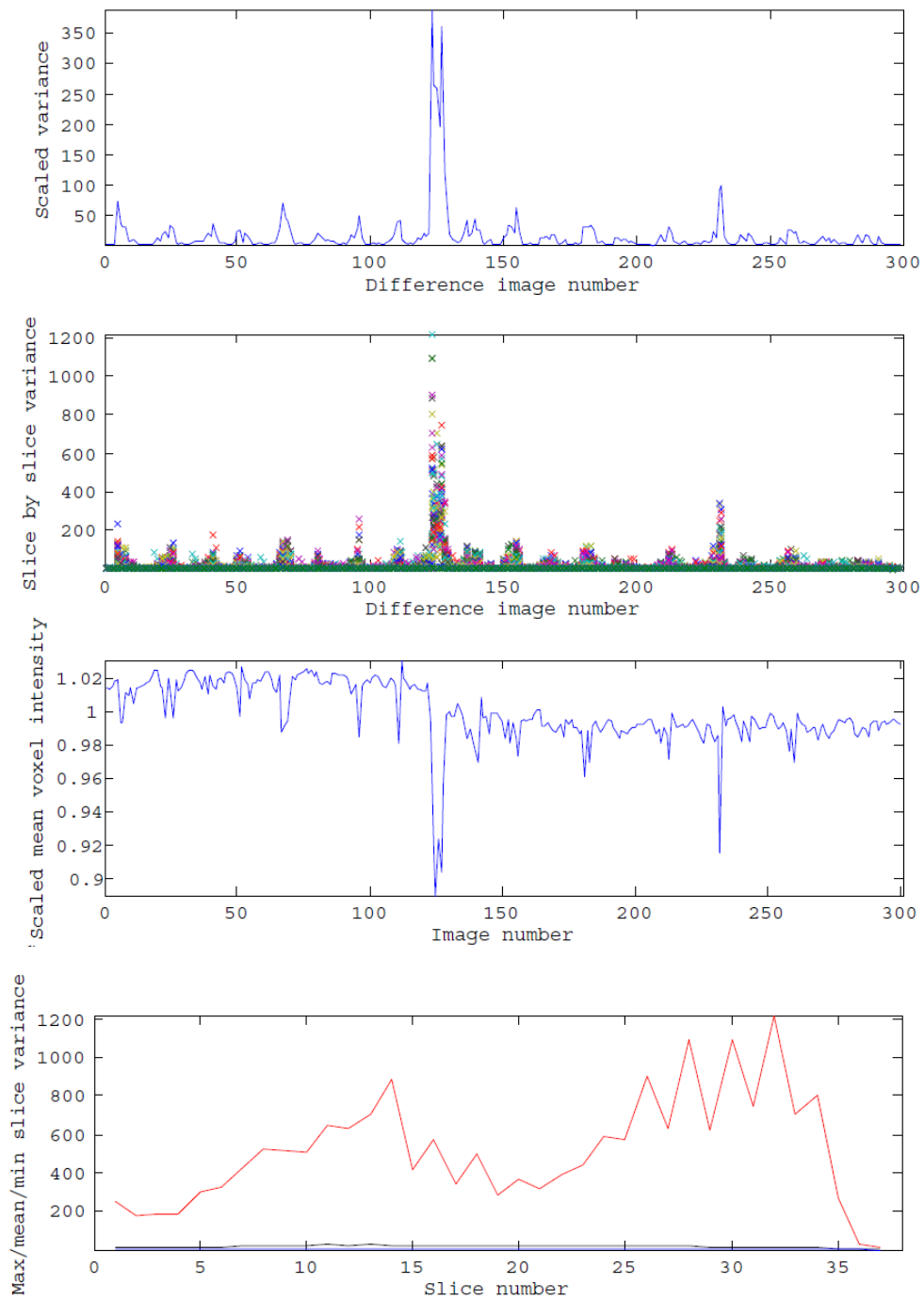


Figure 0-2: Output of TSDiffANA analysis
Demonstrating corresponding spikes in variance between images around 123-128.

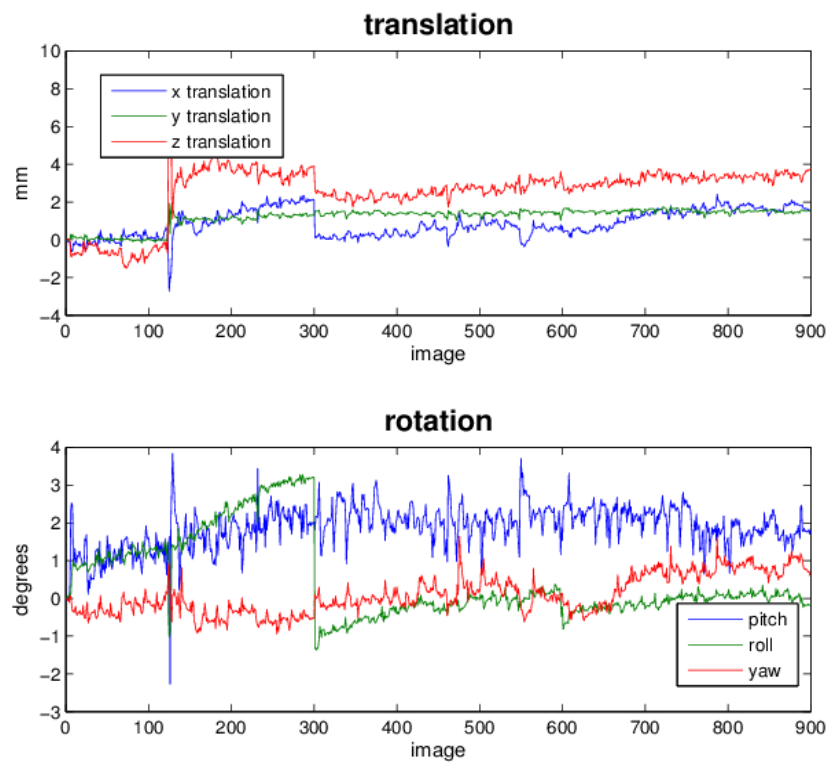


Figure 0-3: Movement output graphs from realignment preprocessing step in SPM8
Demonstrating movement spikes around image 123 – 128.

APPENDIX 3 – COMPUTER SCRIPTS

All code was adapted from scripts written by Dr Adam Hampshire.

MAIN FIRST LEVEL ANALYSIS CODE

```
subs = {'CHUNK05/CHUNK05B/UNC/011189/CH05B_'...
        }%'010874'
nsubs = length(subs);
nsess = 3;
sessname = {'SPAN_1' 'SPAN_2' 'SPAN_3'}
eventroot = '/home/spsljth/Documents/CHUNK'%you will need to change this to
point to a folder containing all of the onsets and durations folders
cnames{1} = { 'STRCORRECT' 'INCSTR' 'RANDCORR' 'INCORRAND' 'CONFCORRECT'
'CONFWRONG' 'NOTCONFCORRECT' 'NOTCONFWRONG'};
cnames{2} = cnames{1};
cnames{3} = cnames{1};
ncond = length(cnames{1});
TR = 2;

dataroot = '/home/spsljth/Documents/CHUNK'%this should point to where your
subject folders are
statsdir = fullfile(dataroot,'stats');
hpf = 180;
incmoves = 1;
modeldur = 1;
imgfilt = '^swa.*\.img$';
movefilt = '^rp.*\.txt$';
mnames = {'x_trans' 'y_trans' 'z_trans' 'x_rot' 'y_rot' 'z_rot'};

%-----
%Design setup
%-----
% basis functions and timing parameters
%-----
-% OPTIONS:'hrf'
%         'hrf (with time derivative)'
%         'hrf (with time and dispersion derivatives)'
%         'Fourier set'
%         'Fourier set (Hanning)'
%         'Gamma functions'
%         'Finite Impulse Response'
%-----
- xBF.name      = 'hrf';
xBF.length     = 32.2;           % length in seconds
xBF.order      = 1;             % order of basis set
xBF.T          = 16;            % number of time bins per scan
xBF.T0         = 1;             % first time bin (see slice timing) -
middle of TA
xBF.UNITS      = 'secs';        % OPTIONS: 'scans'/'secs' for onsets
xBF.Volterra   = 1;            % OPTIONS: 1|2 = order of convolution

failed = {};
for sub = 1:nsubs
    %try
```

```

clear SPM
disp(subs{sub})
SPM.xY.RT = TR;
SPM.xGX.iGXcalc = 'None';
SPM.xVi.form = 'AR(1)';
SPM.xBF = xBF;
csub = subs{sub};

%subdata = fullfile(dataroot, csub);
cd (dataroot)
subdata = fullfile(dataroot, csub)
anadir = [subdata 'DanModelcomplexxtramoves'];
if exist(anadir)~=7; mkdir(anadir);end
cd(anadir);
tc = 0;
allfiles='';
for sess = 1:nsess
    evorder = cnames{sess}
    clear ffiles;

    evdir = [eventroot '/' subs{sub} 'onsets'];
    tc = tc+1;
    sessdata = [subdata sessname{sess}];%+5 to get past other task
    files = spm_select('List', sessdata, imgfilt);
    if incmoves==1
        clear mfname;
        clear moves;
        mfname = spm_select ('List', sessdata, movefilt);
        moves = load(fullfile(sessdata,mfname));
    end

    for f =1:size(files,1)
        ffiles(f,:) = fullfile(sessdata,files(f,:));
    end

    allfiles = strvcats(allfiles,ffiles);
    %essentially, we want to control for any variance that is due to
    %error
    %And capture variance related to uncertainty
    %whilst retatining the originalmodel
    %that means we have 2 main trial type * 3 stages = 6
    %plus an error regressor * 3
    %plus a certainty regressor * 3
    %that makes a total of 12 regressors per level reworked by
    %combining the above text files...

    %cnames{1} = { 'STRCORRECT' 'INCSTR' 'RANDCORR' 'INCORRAND'
    'CONFCORRECT' 'CONFWRONG' 'NOTCONFCORRECT' 'NOTCONFWRONG'};

    for c = 1:12
        if c == 1 %then have all random sequences
            name = 'AllRandE'
            efile1 = [evdir '/RANDCORR_SPAN' num2str(sess) '_1.txt'] ;
            efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_1.txt'] ;
            ons = [];
            try
                ons = [ons load(efile1)];
            catch
            end
            try
                ons = [ons' load(efile2)];
            end
        end
    end
end

```



```

        catch
        end
        durs = ons - ons + 7;
    end
    if c == 2 %then have all random sequences
        name = 'AllStrE'
        efile1 = [evdir '/STRCORR_SPAN' num2str(sess) '_1.txt'] ;
        efile2 = [evdir '/INCORSTR_SPAN' num2str(sess) '_1.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        durs = ons - ons + 7;
    end

    if c == 3 %then have all random sequences
        name = 'AllRandM'
        efile1 = [evdir '/RANDCORR_SPAN' num2str(sess) '_2.txt'] ;
        efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_2.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        efile1 = [evdir '/RANDCORR_SPAN' num2str(sess) '_3.txt'] ;
        efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_3.txt'] ;
        durs = [];
        try
            durs = [durs load(efile1)];
        catch
        end
        try
            durs = [durs' load(efile2)];
        catch
        end
    end
    if c == 4 %then have all random sequences
        name = 'AllStrM'
        efile1 = [evdir '/STRCORR_SPAN' num2str(sess) '_2.txt'] ;
        efile2 = [evdir '/INCORSTR_SPAN' num2str(sess) '_2.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        efile1 = [evdir '/STRCORR_SPAN' num2str(sess) '_3.txt'] ;
        efile2 = [evdir '/INCORSTR_SPAN' num2str(sess) '_3.txt'] ;
        durs = [];
    end
end

```

```

        try
            durs = [durs load(efile1)];
        catch
        end
        try
            durs = [durs' load(efile2)];
        catch
        end
    end

    if c == 5 %then have all random sequences
        name = 'AllRandR'
        efile1 = [evdir '/RANDCORR_SPAN' num2str(sess) '_4.txt'] ;
        efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_4.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        durs = ons - ons + 7;

    end

    if c == 6 %then have all random sequences
        name = 'AllStrR'
        efile1 = [evdir '/STRCORR_SPAN' num2str(sess) '_4.txt'] ;
        efile2 = [evdir '/INCORSTR_SPAN' num2str(sess) '_4.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        durs = ons - ons + 7;

    end

    if c == 7 %then have all random sequences
        name = 'NOTCONF'E
        efile1 = [evdir '/NOTCONF'CORRECT_SPAN' num2str(sess) '_1.txt'] ;
        efile2 = [evdir '/NOTCONF'WRONG_SPAN' num2str(sess) '_1.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        durs = ons - ons + 7;

    end

    if c == 8 %then have all random sequences
        name = 'INCORRECT'E
        efile1 = [evdir '/INCORSTR_SPAN' num2str(sess) '_1.txt'] ;
        efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_1.txt'] ;
        ons = [];

```

```

        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        durs = ons - ons + 7;
    end

    if c == 9 %then have all random sequences
        name = 'NOTCONFM'
        efile1 = [evdir '/NOTCONFCORRECT_SPAN' num2str(sess) '_2.txt'] ;
        efile2 = [evdir '/NOTCONFWRONG_SPAN' num2str(sess) '_2.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        efile1 = [evdir '/NOTCONFCORRECT_SPAN' num2str(sess) '_3.txt'] ;
        efile2 = [evdir '/NOTCONFWRONG_SPAN' num2str(sess) '_3.txt'] ;
        durs = [];
        try
            durs = [durs load(efile1)];
        catch
        end
        try
            durs = [durs' load(efile2)];
        catch
        end
    end
    if c == 10 %then have all random sequences
        name = 'INCORRM'
        efile1 = [evdir '/INCORSTR_SPAN' num2str(sess) '_2.txt'] ;
        efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_2.txt'] ;
        ons = [];
        try
            ons = [ons load(efile1)];
        catch
        end
        try
            ons = [ons' load(efile2)];
        catch
        end
        efile1 = [evdir '/INCORSTR_SPAN' num2str(sess) '_3.txt'] ;
        efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_3.txt'] ;
        durs = [];
        try
            durs = [durs load(efile1)];
        catch
        end
        try
            durs = [durs' load(efile2)];
        catch
        end
    end
end

```

```

        if c == 11 %then have all random sequences
            name = 'CONFR'
            efile1 = [evdir '/NOTCONFCORRECT_SPAN' num2str(sess) '_4.txt'] ;
            efile2 = [evdir '/NOTCONFWRONG_SPAN' num2str(sess) '_4.txt'] ;
            ons = [];
            try
                ons = [ons load(efile1)];
            catch
            end
            try
                ons = [ons' load(efile2)];
            catch
            end
            durs = ons - ons + 7;

        end

        if c == 12 %then have all random sequences
            name = 'INCORRR'
            efile1 = [evdir '/INCORSTR_SPAN' num2str(sess) '_4.txt'] ;
            efile2 = [evdir '/INCORRAND_SPAN' num2str(sess) '_4.txt'] ;
            ons = [];
            try
                ons = [ons load(efile1)];
            catch
            end
            try
                ons = [ons' load(efile2)];
            catch
            end
            durs = ons - ons + 7;

        end

        cnames{sess}(1) = {name};
        SPM.Sess(tc).U(c) = struct(...
            'ons',ons,...
            'dur',durs,...
            'name',{cnames{sess}(1)},...
            'P',struct('name','none'))
    end

    SPM.nscan(tc) = length(ffiles);
    SPM.xX.K(tc).HParam = hpf;
    if incmoves==1
        clear moves2;
        moves2 = zeros(length(moves),6);
        moves2(2:length(moves),:) = moves(2:length(moves),:) -
moves(1:length(moves) - 1,:);
        moves2 = sqrt(moves2.*moves2);
        mnames2 = mnames;
        %the first 3 are translations (4) the second 3 are rotations (0.1)
        for i = 1:SPM.nscan(tc)
            maxtrans = max(moves2(i,1:3));
            maxrot = max(moves2(i,4:6));

            if maxtrans > 4 || maxrot > 0.1
                moves = [moves zeros(SPM.nscan(tc),1)];
                moves(i,length(moves(1,:))) = 1;
                mnames2 = [mnames2 num2str(i)];
            end
        end
    end

```

```

        end

        SPM.Sess(tc).C.C = moves; % [n x c double] covariates
        SPM.Sess(tc).C.name = mnames2; % [1 x c cell] names
    else
        SPM.Sess(tc).C.C = [];
        SPM.Sess(tc).C.name = {};
    end
end

cd (anadir)

SPM.xY.P = allfiles;
SPMdes = spm_fmri_spm_ui(SPM);
spm_unlink(fullfile('.', 'mask.img')); % avoid overwrite dialog
SPMest = spm_spm(SPMdes);

% catch
%     failed(sub) = subs(sub)
%end
end
failed

```

BASIC ANALYSIS CODE FOR CONTRASTS

```
%-----
%Design specific parameters
%-----

%clear
spm_defaults;
subs = { 'CHUNK16/CHUNK16B/UNC/013006/CH16B_' ...
        }%'010874'
nsubs = length(subs);

dataroot = '/home/spsljth/Documents/CHUNK';
for sub = 1:nsubs
    display(sub)
    datadir = [dataroot '/' subs{sub} 'DanModellxtramoves']

    cd (dataroot)
    cd (datadir)

    cons{1} = [0 0 1 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 1 0 0 0 0 0
0 0 0 0 0]
    cons{2} = [1 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0
0 0 0 0 0]
    cons{3} = [1 0 1 0 0 0 0 0 0 0 0 1 0 1 0 0 0 0 0 0 1 0 1 0 0 0 0
0 0 0 0 0]
    cons{4} = [-1 0 1 0 0 0 0 0 0 0 0 -1 0 1 0 0 0 0 0 0 0 -1 0 1 0 0 0
0 0 0 0 0]
    cons{5} = [1 0 -1 0 0 0 0 0 0 0 0 1 0 -1 0 0 0 0 0 0 0 1 0 -1 0 0
0 0 0 0]
    cons{6} = [0 1 0 1 0 0 0 0 0 0 0 1 0 1 0 0 0 0 0 0 1 0 1 0 0 0 0
0 0 0 0 0]

    cname{1} = 'STRENC';
    cname{2} = 'RANDENC';
    cname{3} = 'ALLTRIALSENC';
    cname{4} = 'ALLSTR>RANDE';
    cname{5} = 'ALLRAND>STRE';
    cname{6} = 'ALLRECALL';
clear SPM

    SPMest=load('SPM.mat');
    SPMest=SPMest.SPM;
    % use this to make the con images
    SPMest.xCon = [];
    for i = 1:size(cons,2)
        if length(SPMest.xCon)==0
            SPMest.xCon
            =
spm_FcUtil('Set',cname{i},'T','c',cons{i}',SPMest.xX.xKXs);
        else
            SPMest.xCon(end+1)
            =
spm_FcUtil('Set',cname{i},'T','c',cons{i}',SPMest.xX.xKXs);
        end
    end
    spm_contrasts(SPMest);

end
```

MAIN ANALYSIS CODE FOR CONTRASTS

[illegible]

PPI CODE

```
%addpath /imaging/local/spm/spm5/toolbox/marsbar

% Set paths *****

groupresultsdire = 'home/spsljth/Documents/PPI/PPIresults/';% this is my
directory
batchlocation = (cd('.'));
resultsfolder = ('');
incmoves = 1;
movefilt = '^rp_.*\.txt$';
names = {'x_trans' 'y_trans' 'z_trans' 'x_rot' 'y_rot' 'z_rot'};
moveparamdire = 'onsets';

%set to true to skip stages
skiptimecourse = false;
skipbivarcors = true;
skipPPIs = false;
skipmodels = false;

%for voxelwise analysis
skipcons = true;
skipcollect = true;

%for ROI analysis
skipROIanalysis = false;

%are we really imterested in the whole brain analysis?? if not set this to
%0 and estimate with MarsBaR
VoxelwiseModelEstimateFlag = 0;

cons = [0 0 1 0 0 0 0 0 0 0];%nb don't right pad here, we will add
movements & constant in later
gwd = '/home/spsljth/Documents/CHUNK/';
blocks = {'1' '2' '3'};
nblocks = length(blocks) ;
TR=2;
hpf = 180;

%here we extarct data using the VOI approach for our seed regions
position = {[39 43 33]};
%roi_name = {'left_LOFCsr' 'right_LOFCsr'};%different contrast
roi_name = {'RDLPPC' };
nrois = 1;
radius = 10;%radius of roi in mm

%here we define ROI variables for MarsBaR if we are estimating ROIs not
%Whole Brain
roidirM = '/home/spsljth/Documents/ROI/basicmodelROI/';
roisM = spm_select('List',roidirM,'roi.mat$');
nroisM = size(roisM,1);
roisM = [repmat([roidirM filesep],nroisM,1) roisM]

for r = 1:nroisM
    croiM = deblank(roisM(r,:));
    R{r} = maroi(croiM);
    roi_nameM{r} = descrip(R{r});
end
```

```

% Get subs
*****

%subs = dir(fullfile(statsdir,'CBU0*'));
%subs = dir(fullfile(rootdir,'CBU070502*'));
%subs = cellstr(deblank(char(subs.name)))
%exsubs = {}
%for s = 1:length(exsubs)
%    exi = strfind(subs,exsubs{s});
%    exi = char(exi{:})==' ';
%    subs = subs(exi==1);
%end

%or just define manually*****
subjects={...

    'CHUNK14/CHUNK14A/UNC/012301/CH14A_DanModel1xtramoves' ...
    }%'010874'

nsubjects = length(subjects);

addpath(batchlocation);
if skiptimecourse == false

    cd (batchlocation);
    failedtimecourses = get_VOI_timecourse(subjects, nsubjects, gwd,
blocks, nblocks, resultsfolder, radius, position, roi_name, nrois);

    stage = 'ROI timecourses extracted'
else
    stage = 'ROI extraction skipped'
end

if skipbivarcorrs == false

    cd (batchlocation);
    [failedBiVars, CorrColl] = make_bivarcorrs(subjects, nsubjects, gwd,
resultsfolder, roi_name, nrois, hpf);

    stage = 'BiVarCorrs calculated'
else
    stage = 'BiVarCorrs skipped'
end

if skipPPIs == false
    cd (batchlocation);
    failedmakeppis = make_ppis(subjects, nsubjects, cons, gwd, blocks,
nblocks, nrois, roi_name, resultsfolder);

    stage = 'PPIs calculated'
else
    stage = 'PPI calculation skipped'
end

if skipmodels == false
    cd (batchlocation);
    [failedmakemodels xfiles] = make_models2(subjects, nsubjects, gwd,
blocks, nblocks, nrois, roi_name,TR, hpf, incmoves, resultsfolder,
VoxelwiseModelEstimateFlag);%(subjects, nsubjects, gwd, blocks, nblocks,
nrois, roi_name,TR, hpf, incmoves, movefilt, names, moveparamdir);

```

```

        stage = 'models run'
    else
        stage = 'models skipped'
    end

    if skipcons == false
        cd (batchlocation);
        %failedmakecons =
        make_cons(subjects, nsubjects, gwd, blocks, nblocks, nrois, roi_name,
TR);

        stage = 'contrasts run'
    else
        stage = 'contrasts skipped'
    end

    if skipcollect == false
        cd (batchlocation);
        %failedcollectcons =
        collect_cons(subjects, nsubjects, gwd, blocks, nblocks, nrois,
roi_name, TR, groupresultsdir);

        stage = 'contrasts collected'
    else
        stage = 'contrast collection skipped'
    end

    if skipROIanalysis == false
        [PPI, Phys] = roi_analysis(subjects, nsubjects, gwd, nblocks,
roi_nameM, nroisM, R, roi_name, nrois);

        %kcount = 0;
        %k = zeros(20,30)
        %for a = 1:nrois
        %for b = 1:nroisM
        %kcount = kcount + 1
        %k(:,kcount) = PPI(:,a,b)
        %end
        %end
    else
        stage = 'MarsBaR ROI analysis skipped'
    end

    %failedtimecourses
    %failedmakeppis
    %failedmakemodels
    %failedmakecons
    %failedcollectcons

```

